VOLUME 8 NUMBER 6

ARCHIVES OF PATHOLOGY

DECEMBER, 1929

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of February 28, 1925, authorized Jan. 27, 1926.

ARCHIVES OF PATHOLOGY

VOLUME 8 DECEMBER, 1929 NUMBER 6

VASCULARIZATION OF THE THORACIC AORTA*

H. F. ROBERTSON, M.B.

TORONTO, CANADA

Since Köster drew attention to the relation between the vasa vasorum and the localization of arterial disease, their importance in this rôle has frequently been noted. Ebner and Meigs, following Köster, demonstrated the increasing vasculature of the walls of the blood vessels with disease and the varied manner of advance in different lesions. More recently, Klotz [1] has suggested that the localization of syphilitic lesions in the ascending aorta might have an anatomic basis. He believed that the distribution of inflammatory states within the arterial coats was directly dependent on the vascularity of the walls, and that the senile degenerations of the media were the result of cell starvation, since they were observed distant from the vasa and the intima. Wearn, who found a rich supply of vasa vasorum arising from a coronary branch distributed to that portion of the aortic wall where aortitis is most common, suggested that this relation might have an important significance.

The vasa vasorum of the aortic wall, their origin and anastomoses have been noted for several centuries. Haller [2] mentioned Thomas Willis as one of the first to observe them. The former described them as arising from the right and left coronaries or an accessory coronary, and forming a network in the adventitia of the ascending aorta. This network gives off branches to the media and to the intima; to the pulmonary vasa laterally; to the pericardial vessels and the vasa of the arch above. He described a wide anastomosis between the coronary and the bronchial arteries through the vasa of the pulmonary artery, and the pericardial, internal mammary, inferior thyroid, esophageal and intercostal vessels through the vasa of the ascending aorta. Cruveilhier,[3] Béraud, Langer and lately Gross [4] also observed these

* Submitted for publication, July 22, 1929.

* From the Department of Pathology, University of Toronto.

1. Klotz: Arteriosclerosis, Studies from the University of Pittsburgh, 1911; Tr. A. Am. Phys. **27**:181, 1912; J. Path. & Bact. **18**:259, 1913; J. M. Research **31**:409, 1915.

2. Haller: Elementa Physiologia Corporis Humani Lausanne, 1757, vol. 1, pp. 67-89.

3. Cruveilhier: Descriptive Anatomy, London, 1842, vol. 2, p. 670.

4. Gross: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921; J. Lab. & Clin. Med. **13**:257, 1927.

anastomoses. The vasa of the arch and of the descending limb of the thoracic aorta were described as arising from the aortic lumen or from branches of the bronchial, internal mammary, subclavian, esophageal and intercostal arteries.

Later descriptions agreed closely with Haller's. However, the manner of distribution of the vasa vasorum in the aortic wall proved a debatable point. Bichat [5] found them always ending in the outer third of the media; Meckel found them penetrating to the intima, while Crisp [6] found them ramifying between the adventitia and periadventitia to pierce the media only. Finally, Köster, Ebner, Meigs [7] and Klotz described the vasa vasorum in normal arteries as not passing the outer third of the media, but in disease proliferating and penetrating the inner media to reach the intima.

In 1926, Woodruff [8] found vasa vasorum in the aorta of the horse extending to the intima. In the ascending limb of the dog's aorta, the nutrient vessels were found arising from the lumen directly by discrete openings. One of these was found to anastomose freely with vasa from one of the coronary arteries.

There remains the task of more accurately ascertaining the vascularization of the thoracic aorta, and relating its anatomic character with the processes in disease.

TECHNIC

To accomplish this, the hearts and aortas of dogs, lambs and human beings were studied.

The hearts were injected by aortic cannulae so that the first coronary branches which gave vessels to the aorta were always filled. Celluloid masses of various viscosities were employed, in which finely ground, opaque and colored materials were suspended. An initial air pressure of 300 mm. of mercury suddenly applied was gradually reduced to 150 mm. mercury at the end of one-half hour. Cannulas were then inserted into the coronary vessels, a cinnabar celluloid suspension was injected into the right, and a Berlin blue celluloid suspension into the left, until all large vessels were well filled.

The aortic vessels were filled by injection from the aortic lumen. Glycerin gelatin masses were employed in which finely ground, opaque and colored materials were suspended. An air pressure of 400 to 800 mm. mercury was used. The gelatin was allowed to set while pressure was maintained, so that any untied leaks were stopped while the vessels remained filled.

Radiography, dissection of cleared and uncleared specimens and corrosion of specimens were carried out. Serial sections gave the details of the distribution of the vasa vasorum and other fine vessels.

RESULTS

From the data furnished by these experiments, the thoracic aorta may be roughly described as vascularized by a sheath of areolar con-

5. Bichat: General Anatomy, Boston, 1822, vol. 1, p. 317.
6. Crisp: The Blood Vessels, London, 1847, pp. 3-4.
7. Meigs: Human Blood Vessels, 1907, vol. 2, pp. 25, 70 and 75.
8. Woodruff: Am. J. Path. **2**:567, 1926.

nective tissue richly supplied with blood vessels. This extended from the heart to the diaphragm and below over the abdominal aorta. Over the arch and the descending thoracic limb, this sheath contained at least two distinct layers of interweaving vessels which were derived from vessels of adjacent structures or from branches of the aortic efferent vessels. Over the ascending limb, only a single network was usually seen, derived from coronary branches, from cardiac fat-pad branches of these and from descending vessels of the aortic arch. The adventitial vessels in each case were largely furnished by these anastomotic networks. At the root of the aorta the richest vascular bed was found. The ascending limb was most vascular along its convex border, the arch and the descending limb on their posterior surface.

In order to bring out more clearly the differences in vascularity between the various portions of the thoracic aorta, the features of vascularization common to lamb, dog and man will be described under the headings of ascending limb, arch and descending limb. Points of variance between these mammalian types and interesting differences of vascularization will be noted.

Ascending Limb of Aorta.—The vessels of the ascending limb of the thoracic aorta formed two richly anastomosing networks: one in the connective tissue and fat beneath the visceral pericardium, the other in the adventitia.

The vessels of the periadventitial network usually arose from the first two pairs of branches of the right or the left coronary artery, from branches of these vessels which ran to the conus arteriosus and the pulmonary artery anteriorly, and along the auriculo-aortic grooves and to the superior auricular surfaces posteriorly, or from accessory coronary vessels. From above, the vasa of the arch and the pericardium descended from the pericardial reflection to anastomose extensively with the vessels from below and with aortic branches of the bronchial arteries on the pulmonary artery near its bifurcation (figs. 1 and 2).

From the right coronary artery, the first pair of branches usually ran upward to spread anteriorly and posteriorly over the ascending limb (fig. 1). The anterior branch spread in the aortic pulmonary groove and then over the pulmonary artery, where it frequently anastomosed with pulmonary branches of the left coronary artery. It anastomosed above with vessels encircling the middle third of the ascending limb (fig. 1 *A* and *B*). The posterior branch also anastomosed above with the last mentioned vessel and behind with ascending vessels from the region of the aortic auricular groove (figs. 1 and 2).

The second pair of branches also spread anteriorly and posteriorly (fig. 1). The anterior branch usually constituted the arcuate branch

described by Gross [4] as being the first anterior right coronary division. It supplied the region of the conus arteriosus and anastomosed with a similar branch from the left coronary artery and with adjacent vessels above and below. From it many small branches spread on the wall of the ascending aorta over the anterior sinus of Valsalva. It supplied the fat pads of this portion of the heart with an abundant network of arteriae telae adiposae. The posterior branch usually constituted the ramus osteii cavae superioris of Gross (fig. 1 *D*). It furnished the root of the aorta with many small branches and supplied several vessels to the aortic wall over the right posterior sinus of Valsalva. These

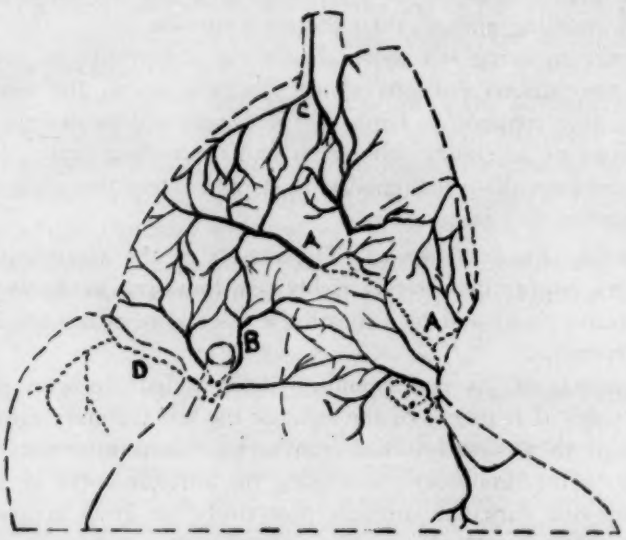


Fig. 1.—The periadventitial network of the ascending aortic limb, anterior view.

latter anastomosed above with the left coronary branch encircling the ascending aorta at its middle third, and anteriorly and posteriorly with nearby aortic vessels.

From the left coronary artery, the first pair of branches usually ran upward and laterally (fig. 2). The anterior branch crossed the aortic pulmonary groove to spread on the pulmonary artery, finally anastomosing with the right coronary branches described. It gave many small twigs to the aortic wall in the region of the aortic pulmonary groove. The posterior branch was generally short. It anastomosed with the vessels arising from the auriculo-aortic groove and with larger vessels above. It supplied an area of the aortic wall a little larger than that lying over the posterior half of the left posterior sinus of Valsalva.

The second pair of branches ran upward and again anteriorly and posteriorly. The anterior branch was found in adult human hearts to

be the largest supplying the aortic wall. It ran at first laterally through the fat about the left coronary opening to the aortic pulmonary groove. Here it turned upward in the areolar connective tissue between the two vessels, and gave numerous branches to each, finally spreading anteriorly on the middle third of the aorta and the pulmonary artery. The former it almost encircled, by passing over its convex surface to unite freely with posterior branches of the left coronary artery over the left posterior sinus of Valsalva. An extensively anastomosing circle of vessels about the middle third of the ascending limb was thus formed (figs. 1 *A* and 2 *A*).

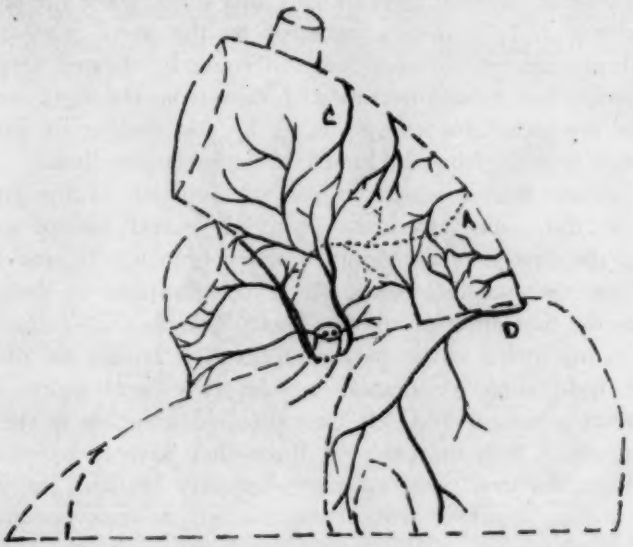


Fig. 2.—The periadventitial network of the ascending aortic limb, posterior view.

The posterior of this second pair of left coronary branches ran almost directly upward from its origin and paralleled the aortic pulmonary groove. It ended just below the pericardial reflection, anastomosing with its vessels and with those on the posterior surface of the aortic arch. It also sent branches laterally into the aortic pulmonary groove and over the pulmonary artery to the left and right, to anastomose with vessels on the convex border of the ascending aorta (fig. 2 *A* and *C*).

From above, the largest vessels descended from the aortic arch (fig. 1 *C*) beneath the pericardial reflection down the convex aspect of the ascending aorta, their branches spreading toward the concave surface and anastomosing with the ascending coronary branches. This anastomosis was especially marked with the left coronary branch which

encircled the middle third of the aorta. Smaller branches from the pericardium and from the posterior surface of the aortic arch and a few bronchial branches on the pulmonary artery descended to anastomose with the vessels described.

The most abundant periadventitial supply to the ascending limb was on its outer aspect. It was considerably less on the posterior aspect and diminished also from below upward, so that the root of the aorta was more abundantly supplied than the portion adjacent to the arch.

As to the variations in the vasculature before noted, the most important was found in the lamb hearts. In these, the large branch from the left coronary, so prominent in man, was small, while the pulmonary vasa and the right coronary branches to the aorta were relatively increased in size. Children's hearts frequently showed this. Dogs nearly always had a preponderance of vasa from the right coronaries. This was accounted for in two cases by the finding of small vasa which arose directly from the lumen of the ascending limb.

The arcuate branch which crossed the junction of the pulmonary artery and the conus arteriosus arose in several human and lamb hearts as the first anterior right coronary branch. It sent branches upward over the ascending aorta which took the place of those usually arising as the first anterior right coronary branch (fig. 1 *B*).

The ramus osteii cavae superioris usually arising as the second posterior right coronary branch was in two lamb hearts and one human heart given off first. It then supplied branches to the ascending aorta which took the place of those that have been described as arising from the first posterior right coronary branch. In one lamb and one human heart it arose from the left coronary as its second branch. It then gave off the vessels which ran over the left posterior sinus of Valsalva and upward just posterior to the pulmonary aortic groove and those described as arising in the auriculo-aortic groove to ascend the posterior aortic wall. The posterior right coronary branches to the aortic wall and the anterior superior aspect of the right auricle were increased in size.

In several hearts a right, and in one heart a left, accessory coronary vessel supplied the areas usually provided for by one or more of the first two pairs of coronary branches.

The adventitial network of the ascending limb was formed by branches of the right and of the left coronary artery below, by branches from the periadventitial network and from the adventitial vessels of the arch. They arose from the first four right and left coronary branches as fine vessels, at first in the cardiac fat pads, later ramifying above in the adventitia. In this, they spread on the ascending aorta over an area corresponding to the anterior and the left posterior sinuses of Valsalva, anastomosing above with the vessels given off by the

periadventitial network. At the root of the aorta, vascularization was most abundant over the anterolateral aspect and least abundant behind over the right posterior sinus of Valsalva.

Finally, the outer third of the media was supplied by branches of those networks which penetrated it at right angles, to spread laterally and longitudinally between the elastic lamellae. These branches anastomosed freely. They were largest and more closely grouped near their parent vessels. Those more distant were smaller, had longer branches with fewer anastomoses and were obliged to supply a greater portion of the aortic wall. The medial vessels were grouped more closely and were more numerous at the convex surface and about the root of the aorta over the region of the left posterior and the anterior

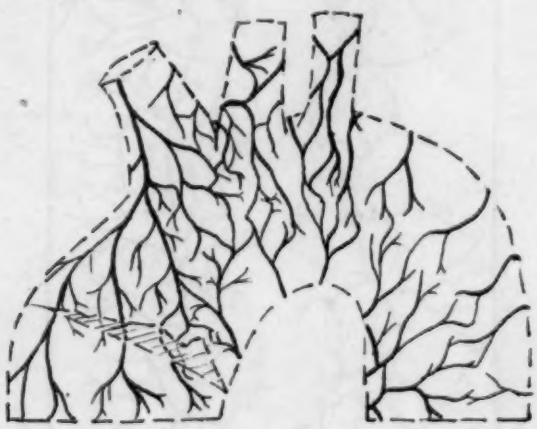


Fig. 3.—The periadventitial network of the arch of the aorta, anterior view.

sinus of Valsalva. They were most numerous immediately beneath the adventitial or periadventitial vessels, diminishing in number between them.

Arch of Aorta.—The periadventitial network of the arch could be divided into two layers: one in the areolar connective tissue, the other lying on the adventitia.

The outer periadventitial network arose superiorly from branches of the innominate, left carotid and subclavian arteries which descended and ramified over it. These branches arose at various distances above the arch, usually at least half an inch (1.27 cm.). The largest vessel descended from the right anterolateral surface of the innominate artery to ramify on the convex surface of the ascending limb as described (figs. 2 and 3). The branches from the other great vessels were smaller and were less numerous especially toward the descending portion of the arch. Posteriorly, a thick periadventitial network was

formed, deriving its vessels from the inferior thyroid arteries, the esophageal and upper intercostal branches of the aorta and the bronchial arteries. The superior and the posterior periadventitial vessels terminated or anastomosed with each other along the midline of the anterior aortic surface.

The inner periadventitial network was formed by branches of the outer group. About the great vessels of the neck and the first pair of intercostal vessels, however, branches were given to it directly. Its larger vessels followed the course of those in the layer above, although they were usually not found lying directly beneath them. They anastomosed frequently, forming loops about the roots of the great vessels.

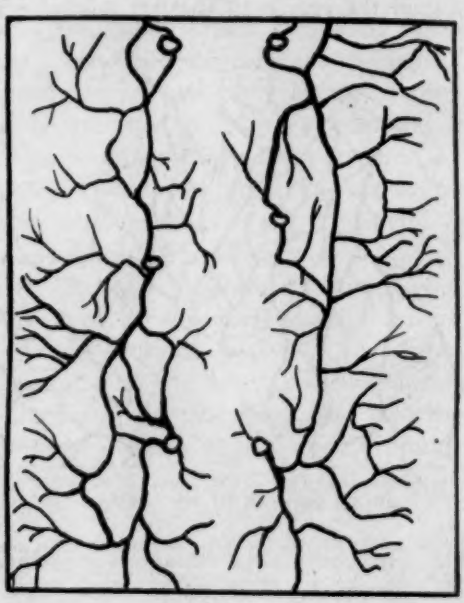


Fig. 4.—The distribution of the vessels of the descending thoracic limb of the aorta: outer periadventitial network.

The vasa vasorum were finally derived from these two outer networks to form an adventitial network and then penetrated the outer third of the media as described. They were most numerous beneath the periadventitial ramifications.

The vascularity of the arch was greatest on the convex surface of its ascending portion, and on the posterior surface of its transverse portion (fig. 3). It was least vascular on its anterior surface, particularly toward its descending portion. This latter section was most vascular on its posterior aspect, resembling the descending thoracic limb in this respect.

Descending Limb of Aorta.—The two periadventitial networks of this portion were formed by vessels which usually arose from the branches of the aorta at least 2 mm. beyond its adventitia. The inferior thyroid arteries and the periadventitial vessels of the arch supplied the upper end of the descending limb with many branches.

The more superficial network spread from vessels which looped longitudinally between each pair of intercostal vessels (fig. 4). Their branches ramified laterally over the anterior aortic wall, and for a short distance toward the midline of the posterior wall. Longitudinally there was extensive anastomosis. Fluid injected into the upper intercostals often appeared in one of the lower intercostal mouths. Laterally,

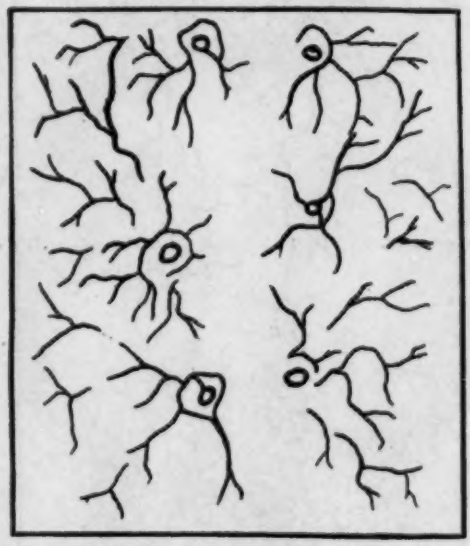


Fig. 5.—The distribution of the vessels of the descending thoracic limb of the aorta: inner periadventitial network.

the ramifications over the anterior wall of the aorta did anastomose, but not so plentifully.

This outer periadventitial network supplied vessels to the inner, the vessels of which ran over the adventitia paralleling closely the larger vessels from which they arose. They formed vascular collars about the aortic vessels (fig. 5). From these they received many branches, given off usually 2 mm. beyond the adventitia as described, and running back to spread on the aorta and encircle the parent vessel. No individual vessel of this deeper network could be followed for more than a short distance, but together they formed a network approximating in appearance the more superficial one. Longitudinally, anastomoses

were extensive, but in the specimens studied the network was not continuous laterally for more than a few centimeters.

From these vascular networks, the adventitia and the media were vascularized by branches forming a network in the adventitia, this in turn supplying the outer third of the media as described. The most numerous branches to the media surrounded the smaller branches of the aorta, particularly the intercostals. Here they formed several anastomosing sheaths and arborescent groups about each vessel. Some of the branches lay in the adventitia between the media of the aorta and that of its efferent branches, to spread in the media and almost reach the

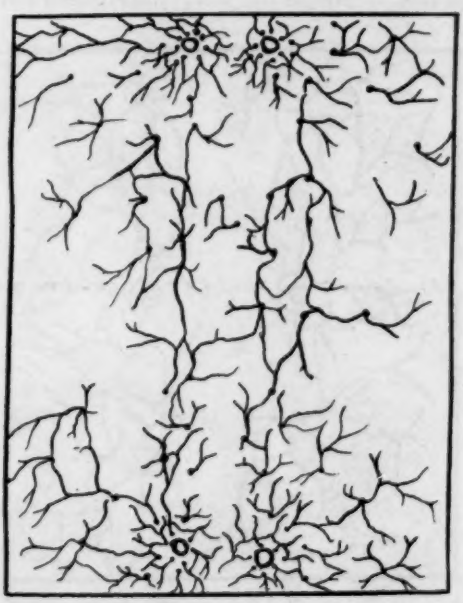


Fig. 6.—A diagram illustrating the distribution of the vasa vasorum of the descending thoracic limb to the media (cut on the flat).

intima; none accomplished this in healthy tissue. Others pierced the media at intervals of from about 20 to 60 microns, and as the distance from the efferent vessel increased, these intervals became greater. Also the number of penetrating vessels decreased, their longitudinal and lateral branches between the elastic fibers increasing in length. Over the posterior wall of the aorta at points central to the efferent branches the number of vessels was least and their separation greatest. Beyond the posterior aspect of the aorta a similar vasal supply to the media was seen, while anteriorly there were barely half as many of these branches in a low power field as there were in a line connecting two of the intercostal branches (figs. 6 and 7).

The descending aortic limb and its connective tissue sheath were most abundantly supplied with vessels, along two longitudinal strips just lateral and parallel to the efferent vessels. The vasa vasorum were most numerous beneath these areas and also in regions encircling each efferent vessel.

The vasa of the thoracic aorta have been described as usually arising from its branches, and the vessels penetrating to the media as arising from the adventitial network. Several variations in this arrangement were found.

The discrete openings in the ascending aorta of the dog, found by Woodruff,[8] were noted in two dogs. They were situated on the right

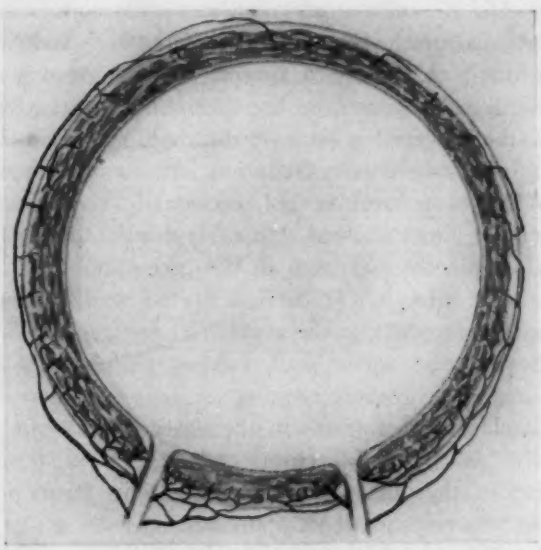


Fig. 7.—A diagram illustrating the distribution of the vasa vasorum of the descending thoracic limb to the media, as seen in a cross-section of the thoracic aorta.

anterolateral surface of the aortic wall, in an area occupying longitudinally the middle third of the ascending limb. Three of the vessels ran from the intima to the vasa arising from the coronary arteries and the aortic arch. Two of them pierced the intima to spread in the media.

The vasa described in the aorta of the horse by Woodruff as penetrating as far as the intima were not found in this study except when the media and the intima were diseased. Atheromatous areas of the intima were frequently completely encapsuled by vessels penetrating from the media. However, two sections from human aortas showed minute nutrient vessels penetrating the intima and branching in the inner third of the media.

Frequently, the vasa vasorum arose from the branches of the aorta while passing through its wall. This they entered at the junction of the media and the adventitia to send branches into the media and along the adventitia to anastomose with the other vasa. The media was not penetrated directly by these branches (fig. 7).

The periadventitial vessels were frequently found to send branches to the media directly. These branches, after giving off their adventitial branches, spread out in the media.

COMMENT

The foregoing description of the vascular distribution to the aorta is of interest in relation to the localization of aortic disease. Aneurysm was stated by Osler [9] to be most frequent on the convex border of the ascending aorta and on the posterior part of the arch and the descending limb. Klotz found, in a study of autopsies in 501 cases with aneurysm, that in 207 the lesion occurred on the ascending limb, in 86 on the arch and in 36 on the descending limb of the thoracic aorta. Aneurysm is thus most frequent where vascularization is most abundant.

The blood stream itself is not necessarily the direct carrier of injurious agents. Klotz showed that in syphilitic aortitis, which is the disease most frequently met with in the ascending limb and the arch of the aorta, the infection is carried to the wall by the lymphatics following the blood vessels of the aorta. In general, the distribution of the lymphatics of the aortic wall follows closely that of the vasa vasorum.

Nodular endarteritis appears in the descending aorta and becomes most advanced about the intercostal openings. The posterior border of this portion of the aorta is the site second in frequency. In these areas the vasa vasorum are most abundant.

The appearance of adolescent or early adult aortas showing superficial fatty streaks suggests a relation between the vasa vasorum and the localization of intimal fatty change. The aortas show the fatty deposit most prominently at the intercostal openings and along the base. In the latter region, they delineate the longitudinal lines between the intercostal orifices beneath which the vasa vasorum are most abundant (fig. 4). When chronic nodular endarteritis has thickened the intima around the intercostal openings, these areas are fat-free. As middle life is approached or as aortic disease becomes advanced, superficial fatty streaks are less frequently seen. Only remnants of former fatty deposits appear about the intercostal openings or over patches of intimal and medial fibrosis and degeneration. This is possibly due to a deple-

9. Osler and McCrae: Principles and Practise of Medicine, New York, P. Blakiston's Son & Company, 1926, p. 869.

tion of the fluid exchange in these regions, the outcome of the fibrosis of antecedent aortic lesions.

Glasunow in his imbibition experiments showed that the dye was absorbed most readily on the posterior wall, along the longitudinal lines delineating the vasa vasorum between the intercostal arteries. Some of his specimens closely resembled adolescent aortas with superficial fatty streaks.

It is probable that the localization of intimal lesions of toxic, nutritional or metabolic origin depends on the variations in absorbing power of different regions of the inner aortic wall. The latter, in turn, seems to be determined by the degree of vascularization.

The medial changes characteristic of toxic and infectious conditions of the aorta are most frequent near the intercostal vessels and about the vasa vasorum. Whether the lesion is primarily lymphatic or vascular is not always ascertainable. In either case, distribution of the vasa vasorum seems to determine the localization of the lesion. In adventitial lesions, this observation has been commonly made.

The senile changes of the media are most frequent where the vasal supply is least. As Klotz pointed out, this probably depends on the decreased nutrition of these areas.

SUMMARY

The vascularization of the thoracic aorta has been described, and its relation to disease discussed.

Blood vessels are found to be most numerous in the aortic wall where aortic disease, other than senile change, is the most commonly localized.

A relation exists between the presence of certain lesions of the aortic wall and the distribution of the vasa vasorum.

The technic here outlined differed from the methods [10] formerly employed, in that the pigment and radio-opaque material was in the form of a stable suspension. The coronary branches to the ascending limb of the aorta were not occluded by coronary cannulae and were therefore filled and demonstrable.

---

10. Campbell: Quart. J. Med. **86**:247, 1929. Whitten, M. B.: Review of Technical Methods of Demonstrating Circulation of Heart; Modification of Celluloid and Corrosion Technic, Arch. Int. Med. **42**:846 (Dec.) 1928.

AN UNUSUAL TYPE OF TRIATRIAL HEART*

B. M. PATTEN, PH.D.
AND
W. B. TAGGART, M.D.
CLEVELAND

The unusual degree to which congenital defects of the heart have interested both laboratory and clinical workers is attested by the voluminousness of the literature on the subject. The fact that many of the seemingly innumerable communications are scattered in publications difficult of access makes one hesitate to state that any cardiac anomaly, no matter how unique it seems, has not been previously seen and perhaps carefully described; but a diligent search of the literature has not yielded any instance of the peculiar malformation recently presented by a patient at the Babies and Childrens Hospital of Cleveland. Its apparent uniqueness as far as structural conditions and course of circulation are concerned and especially its interesting embryologic bearings seem to make it worth adding to the many bizarre distortions of normal heart development already on record.

REPORT OF CASE

Clinical History.—A white girl, 3 months of age, the second of two children, had been born at full term, weighing 6½ pounds (2.9 Kg.). Abnormally rapid respiration and cyanosis had been constantly present since birth. For two days prior to admission, fever, irritability and frequent green stools had been noted.

The child was undernourished, weighing but 3.9 Kg. On admission, the temperature was 38 C. (100.4 F.), rising in the next few hours to 40 C. (104 F.). Cyanosis was extreme, especially in the mucous membranes and in the extremities, which were noticeably cold. Respiration was rapid, shallow and panting. The rate varied, with marked, irregular, periodic tachypnea. There was slight retraction of the head, but no rigidity. Mucopurulent material was found in the fauces, and one ear drum was slightly hyperemic.

The veins of the neck were prominent. The liver extended to the umbilicus. The chest showed scattered moist râles, most pronounced at the left base, with harsh breath sounds over the entire chest, especially posteriorly. At the angle of the left scapula, the breath sounds were bronchial. The percussion note was resonant, except for an area of impairment at the left apex anteriorly.

Cardiac activity was increased in intensity and extent. A systolic impulse and diastolic impact were palpable over the right ventricle. The area of cardiac dulness extended from 1 cm. to the right of the right sternal margin to slightly outside the left midclavicular line at the fifth rib. The upper border of dulness was continuous with the areas of impaired resonance at the left apex. A widely distributed, loud systolic murmur was most pronounced just to the right of the apex

* Submitted for publication, Sept. 26, 1929.

* From the Departments of Histology and Embryology, and of Pediatrics, School of Medicine, Western Reserve University, and from the Babies and Childrens Hospital of Cleveland.

pulsation. The rate was rapid, and tick-tock sounds like those usually associated with cardiac anomalies were heard. The blood was of a darker color than could be registered with a Tallqvist scale, and showed a white cell count of 20,000. The urine showed a trace of albumin.

Roentgen examination showed the heart shadow to be globular. The hilums showed increased shadows, presumably due to either bronchopneumonia or pulmonary hyperemia.

Dyspnea became progressively more marked, and the patient died thirty-three hours after admission. The diagnosis, both clinical and roentgenologic, was congenital defects of the heart.

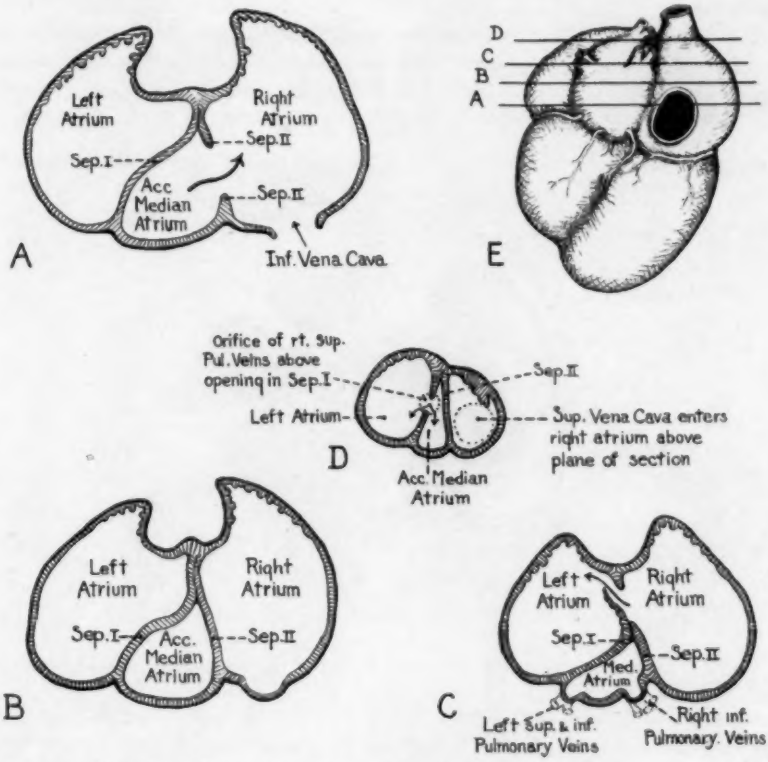


Fig. 1.—Diagrams illustrating the relationships of the accessory median atrial chamber. The lines *A* to *D* on the sketch of the dorsal aspect of the heart show the levels of the accompanying schematic cross sections. Note that three coronary veins, as well as the pulmonary veins, open into the median chamber. A coronary valve fairly normal in appearance and location (compare with fig. 2) covers nothing but a blind pocket at the point where the coronary sinus should appear. The septums have been labeled with their embryologic names, septum primum and septum secundum.

Necropsy.—Aside from the conditions in the heart, which are described in detail later, the following positive observations were made post mortem: generalized livor mortis, peritoneal fluid containing a few shreds of fibrin, bilobed right lung with some areas of atelectasis and a left lung of normal configuration but with extensive atelectasis. The liver was large and showed some evidence of

chronic congestion. Similar changes were present also in the spleen. The intestinal tract showed some hyperplasia of the lymphoid structures, with slight irregular injection of the mucosa. No other pathologic conditions were found.

The heart weighed 51 Gm. Externally, it showed a marked dilatation of the right ventricle and a definitely enlarged pulmonary trunk. Viewed in dorsocaudal aspect, it revealed a median bulging of the atrial region marked off on either side by fairly definite lines of depression (fig. 1 *E*). When the heart was opened, this dilatation was found to mark the presence of an accessory median atrial chamber. The external depressions bounding it were indications of the attachments of septums separating this accessory chamber from the right and left atria, respectively.

The accessory chamber was roughtly wedge-shaped, with its bulging base presenting on the dorsocaudal wall of the atrium and the apex of the wedge directed ventrocephalically (fig. 1). Both left pulmonary veins opened by a common funnel into this median chamber, as did also the group of three right inferior

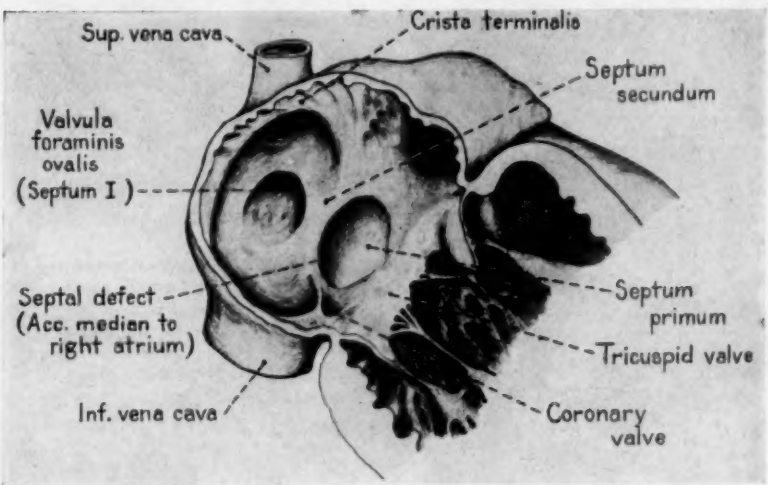


Fig. 2.—Drawing of the heart opened to show the interior of the right atrium. The defect in the septum which separates the median from the right atrium, allows one to look into the median atrium and see the septum which separates it from the left atrium (fig. 1 *A* may be compared here). This septum which forms the left wall of the median chamber exhibits the relations to the atrioventricular canal septum which are absolutely characteristic of septum primum in the embryonic heart.

pulmonary veins (fig. 1). The right superior pulmonary veins entered near the apex of the wedge, astraddle of a small defect[1] in the septum separating the accessory median, from the left atrial chamber (fig. 1 *D*). Measurements of the outlets of the pulmonary vein made with a calibrated cone, indicated that approximately one tenth of the total pulmonary return could thus enter the left atrium directly.

---

1. Instances of the opening of either the superior vena cava or the right pulmonary veins astride of a septal defect which gives the entering blood access to either atrium have been reported by: Chiari (Einmündung der rechtsseitigen Pulmonalvenen im rechten Vorhof. Defecte im Septum Atriorum, Jahrb. f. Kin-

Superiorly, the apex of the wedge-shaped accessory chamber did not extend all the way to the cephaloventral wall of the atria (fig. 1 *B* and *C*). There was thus a place in which the right and left atrial chambers were not separated from each other by the accessory median chamber. In this region there was an oval orifice in the right-hand septum, guarded only by a loose flap of the left-hand septum (fig. 1 *C*) which would permit blood to pass freely from the right atrium to the left. Although this orifice was perhaps a little farther from the inferior caval opening than was normal, its relations clearly placed it as the foramen ovale (fig. 2).

COMMENT

The astonishing circulatory paths presented by this heart are diagrammatically summarized in figure 3. Nine tenths of the blood returning from the lungs entered the accessory median atrium, which was virtually cut off from the left side of the heart. From this median chamber, the blood passed through a large septal defect (117 sq. mm.) into the right atrium. Thence it was distributed between the enlarged right ventricle, which must have received the major share, and the left atrium, which could receive mixed blood through an open foramen ovale (functional orifice 30.2 sq. mm.). The mixed blood thus entering the left atrium was enriched by the direct entrance of but a small fraction (approximately one tenth) of the blood returning from the lungs. This almost negligible contribution of fully oxygenated blood was delivered by the right superior pulmonary vein which opened astride of a small hole (3.2 sq. mm.) in the left septum near the foramen ovale. The enlarged pulmonary artery contributed to the deficient volume of the systemic circulation over an open ductus arteriosus, but the mixed blood thus brought into the aorta could have been of small help in relieving the oxygen deficiency in the systemic circuit.

The enlargement of the right side of the heart may be attributed to the excess of blood entering on that side; for the right atrium received not only the normal caval return, but also, by way of the septal defect, most of the blood that should have gone to the left atrium. The enlarged right ventricle and the oversized pulmonary artery would naturally follow. The same conditions which increased the volume of blood received by the right side of the heart entailed a corresponding decrease in the blood volume received by the left side of the heart.

---

derh. **15**:319, 1880); Geddes (Abnormal Superior Vena Cava, Anat. Anz. **41**: 449, 1912); Hepburn (Double Superior Vena Cava, Right Pulmonary Veins Opening into Right Auricle and a Special Inter-Auricular Foramen, J. Anat. & Physiol. **21**:438, 1887); Ingalls (Vena Cava Superior Receiving Two Upper Right Pulmonary Veins and Opening into Both Atria, Bull. Johns Hopkins Hosp. **18**:136, 1907); Wagstaffe (Two Cases of Free Communication Between the Auricles by Deficiency of the Upper Part of the Septum Auriculorum, Tr. Path. Soc. London **19**:96, 1868). Such cases are of incidental interest in connection with the unusual mode of entrance of the right superior pulmonary veins in the case under consideration.

The small capacity of the left atrium and ventricle, the underdeveloped ventricular musculature and the undersized aorta were the inevitable consequences.

The inefficiency of this cardiovascular mechanism which was constantly sending to the lungs blood already partially saturated with

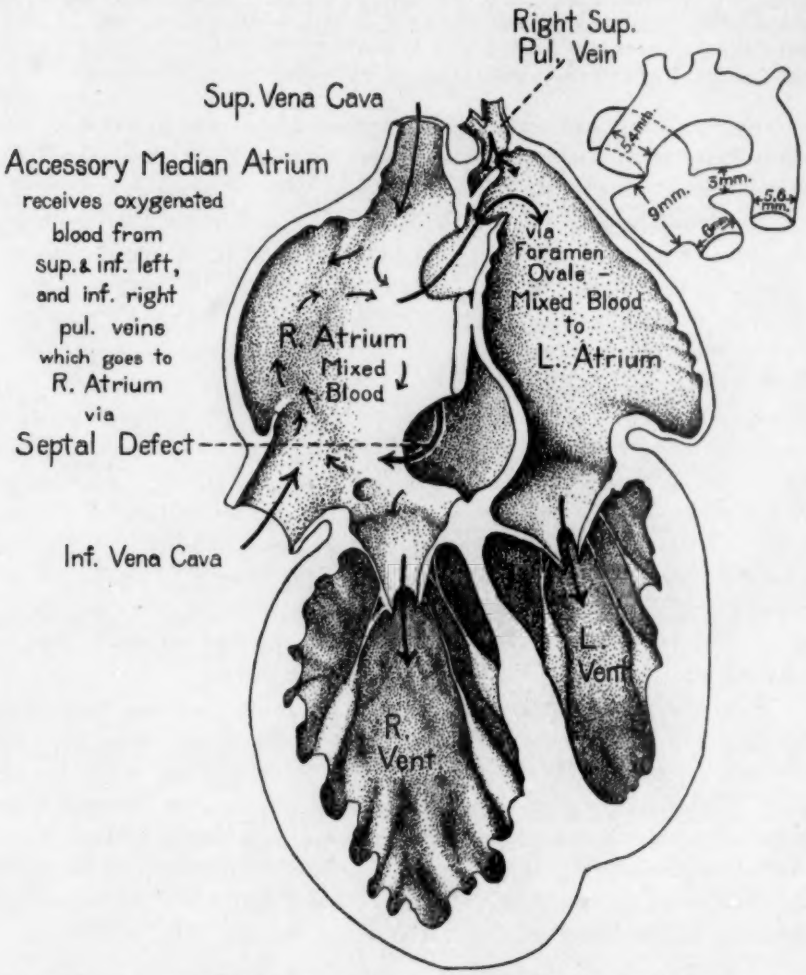


Fig. 3.—Schematic diagram of the dorsal half of the heart laid open to show the course of the circulation through the three atrial chambers. The relative sizes of aorta, pulmonary artery and ductus arteriosus are indicated by the sketch inserted in the upper right hand corner of the illustration.

oxygen, and to the systemic circulation blood deficient in oxygen and overloaded with carbon dioxide was clearly indicated by the rapid gasping respiration and the marked cyanosis. The surprising thing is not that such a mechanism failed to support life, but that the infant with it was able to survive for as long as three months.

EMBRYOLOGIC INTERPRETATION

We cannot rule out the possibility that there may be certain types of congenital defects that are of purely hereditary origin. The high incidence of structural variations in offspring produced following the irradiation of parental gonads (Little and Bagg;[2] Muller[3]) indicates that disturbances in the gametes themselves may determine certain structural anomalies before intra-uterine life has commenced. But it seems highly improbable that all or even most anomalies are thus irrevocably fixed at the time of fertilization.

Increasing evidence is being accumulated that disturbances in the living conditions of a growing embryo can and do produce developmental distortions (Mall,[4] Mall and Meyer[5]). Furthermore, it is known that the same disturbing factor, applied under experimental control at different stages of development, produces not the same but different anomalies (Stockard[6]). This seems to mean that the nature of the distortion so produced depends on what developmental happenings were in a rapidly progressing and, therefore, sensitive and readily modifiable stage (Hyman[7]) when the disturbance in the embryo's living conditions occurred, rather than on the nature of the disturbance itself. It seems not impossible that further experimental work along these lines may lead to the recognition of disturbing factors in intra-uterine environment that can be controlled. It may, therefore, become of more than academic interest to know at precisely what stage of development a given type of malformation had its incipience.

In spite of the extraordinary functional picture presented by the heart under consideration, the nature of the embryologic distortion which must have produced it does not appear so obscure as one might, at first glance, believe. Normally, there are formed, in the partitioning

---

2. Little, C. C., and Bagg, H. J.: The Occurrence of Four Inheritable Morphological Variations in Mice and Their Possible Relation to Treatment with X-Rays, J. Exper. Zool. **41**:45, 1924.

3. Muller, H. J.: The Production of Mutations by X-Rays, Proc. Nat. Acad. Sc. **14**:714, 1928.

4. Mall, F. P.: A Study of the Causes Underlying the Origin of Human Monsters, J. Morphol. **19**:1, 1908; On the Frequency of Localized Anomalies in Human Embryos and Infants at Birth, Am. J. Anat. **22**:49, 1917.

5. Mall, F. P., and Meyer, A. W.: Studies on Abortuses: A Survey of Pathologic Ova in the Carnegie Embryological Collection. Contrib. Embryol. **12**: 1, 1921.

6. Stockard, C. R.: Developmental Rate and Structural Expression: An Experimental Study of Twins, "Double Monsters" and Single Deformities, and the Interaction Among Embryonic Organs During Their Origin and Development, Am. J. Anat. **28**:115, 1921.

7. Hyman, L. H.: The Metabolic Gradients of Vertebrate Embryos: IV. The Heart, Biol. Bull. **52**:39, 1927.

of the originally common atrial chamber, two interatrial septums. Following the terminology of Born [8] one commonly designates these as interatrial septum primum (or septum I) and interatrial septum secundum (septum II). Septum primum has normally made its appearance as a crescentic partition on the cephalodorsal wall of the primitive common atrium by the end of the first month of development. (It is well formed in 4 mm. embryos.) By the end of the second month, septum primum meets and fuses with the atrioventricular canal cushions which divide the primitive atrioventricular canal into right and left channels. Just before this fusion occurs, it seems as if the two atria were destined to be prematurely separated, leaving the left side of the heart with no entering blood save an insignificant trickle from the

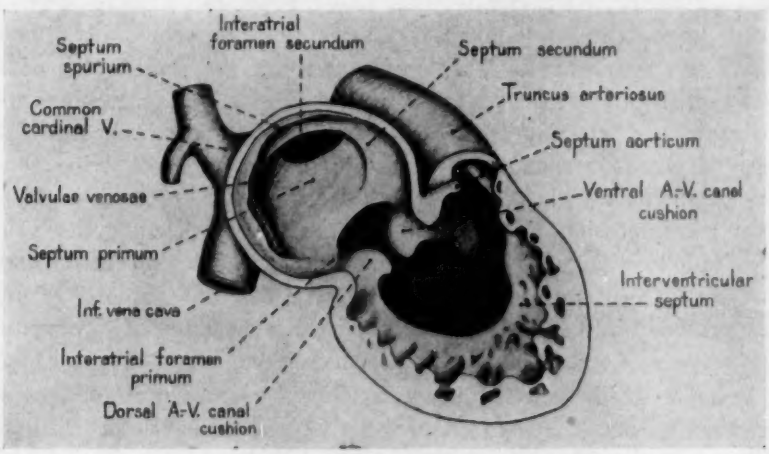


Fig. 4.—Drawing illustrating the relations of septum primum and septum secundum in the embryonic heart. (Semischematic combined illustration, in part from the figures of Born and Tandler and in part from reconstructions and dissections by one of us.) If one imagines septum primum starting to form abnormally far to the left, so that it grows all the way to the atrioventricular canal cushions without becoming fused with septum secundum, the condition exhibited by the abnormal heart under consideration would be established (compare with fig. 2).

developing pulmonary veins. But at this critical time, a secondary opening appears in septum primum. This secondary opening (the ostium secundum of Born), formed by the local disintegration of septum primum near its point of origin from the cephalodorsal wall of the atrium, permits continued access of blood to the left atrium (fig. 4).

Meanwhile a second interatrial partition has started to form immediately to the right of septum primum. Like the septum primum when

8. Born, G.: Beiträge zur Entwicklungsgeschichte des Saügethierherzens, Arch. f. mikr. Anat. **33**:284, 1889.

it first appeared, the newly formed septum secundum is of crescentic shape with its concavity directed toward the atrioventricular canal (fig. 4). The tips of the crescent, however, instead of reaching all the way to the atrioventricular canal, blend with septum primum. Thus, if septum primum is defective and fails to close off the original interatrial communication, septum secundum does not complete the partition, and there remains a characteristically located septal defect (fig. 5). The fact that it is septum primum rather than septum secundum that forms the portion of the definitive interatrial septum near the orifices of the atrioventricular canal has, if recognized at all, received little emphasis. It seems to us the key at once to defects of the type shown in figure 5, and to the more complex conditions in the heart under discussion.

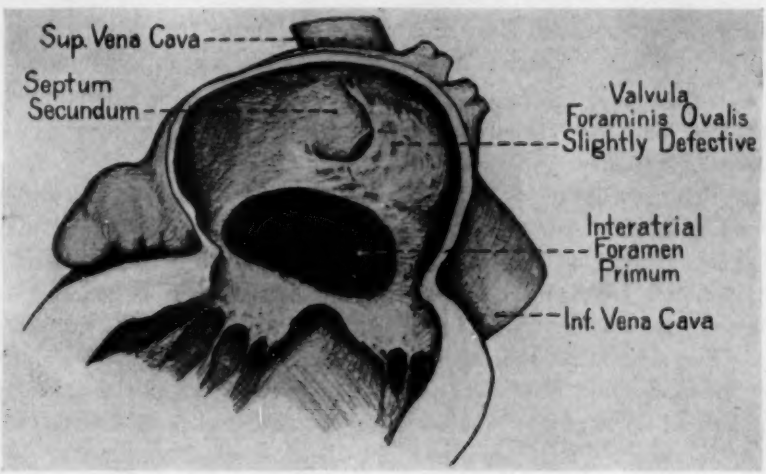


Fig. 5.—Heart showing a large septal defect in the region occupied by the interatrial foramen primum of embryonic life (drawn from specimen no. 264, in the museum of the Pathologisch-anatomisches Institut, Vienna). The case, in a boy, aged 19, was described but not illustrated by Rokitanski (Die Defecte der Scheidenwände des Herzens, Vienna, Wilhelm Braumüller, 1875; his case 4). It exemplifies a not uncommon type of interatrial defect of interest in this connection because it shows the way in which septum secundum fails to grow to the atrioventricular canal independently, when there is an arrest in the development of septum primum. In our case, displacement of septum primum so far to the left that septum secundum cannot fuse with it has apparently produced the same results that are encountered when septum secundum lies in the normal relation to an arrested septum primum. In both cases, lacking the lead of septum primum, septum secundum fails to reach the atrioventricular canal cushions. (Compare figs. 2, 4 and 5.)

The extension of septum secundum takes place mainly toward the orifice of the inferior vena cava. Its growing margins bound a rounded opening, the foramen ovale, which becomes reduced in size as development progresses, but which is never obliterated. On the left side of

septum secundum, the remains of septum primum lie as a loose flap covering the foramen ovale and acting as a one-way valve, which is readily pushed aside by blood pressure from the right, but which closes the orifice on pressure from the left. Thus, in the fully formed heart, the interatrial septum is, superiorly, the septum secundum of embryonic stages, while toward the atrioventricular canal, septum primum and septum secundum become fused with each other, septum primum contributing certainly the major portion, if not all, of this part of the definitive septum. Above the fusion, septum primum remains until after birth as an independent flap, the valvula foraminis ovalis. After the foramen ovale is anatomically closed, as normally occurs late in the first postnatal year, the limbus fossae ovalis still marks the old margin of the embryonic septum secundum. On the left atrial side, close inspection of the septum will show the crescentic line of the old free margin of septum primum where it has become fused to septum secundum.

What originally started the heart under consideration off the normal path that has been briefly outlined, one can only conjecture. The embryologic interpretation of the structures present seems, however, clear. The septum between the accessory median chamber and the left atrium is septum primum. Its free upper margin serving as a valvula foraminis ovalis (fig. 1*C*) and its basal attachment to the atrioventricular canal septum (fig. 3) are absolutely characteristic. It is peculiar only in having its origin from the dorsal atrial wall abnormally far to the left. The septum between the median chamber and the right atrium is septum secundum. The oval foramen, the relations of the crista terminalis and those of the caval and coronary valves are all characteristic (figs. 1 and 2). It is abnormal only because of the existence of an opening, located just above the base of the atrioventricular valves and communicating with the accessory median chamber.

A similarly located defect in an otherwise fairly normal heart is shown in figure 5 for comparison. The opening in both cases is in that part of the definitive interatrial septum which we believe to be formed normally by the septum primum. In the heart with but the normal two atria, we would interpret the defect as being due primarily to failure of septum primum to reach the atrioventricular canal partition. Later, when septum secundum fused with septum primum, it did not carry the lower border of the interatrial partition beyond the level at which septum primum was arrested, thus leaving the primary interatrial ostium permanently open. In our case, septum primum has grown all the way down to and fused with the atrioventricular canal cushions, but it was so far displaced to the left at this point that septum secundum could not fuse with it. Thus, although septum primum has completely obliterated the primary interatrial ostium, there remains a gap at the

base of the interatrial septum where defects due to failure to close ostium primum ordinarily appear. This condition would seem to offer unusually good confirmation of the view that the definitive interatrial septum in this region is formed primarily by septum primum rather than by septum secundum, for there is in this case a septal defect due not to deficient growth of either septum I or septum II, but to the accident which separated the two in a region where they normally complement each other.

Looking at this curious heart from another standpoint may help to make its interpretation clear. If one visualizes septum primum as retaining ventrally the relations shown in the section diagrams of figure 1, but having its dorsal attachment swung over against septum secundum one has practically a normal heart. The accessory median chamber would be obliterated, the pulmonary veins would empty as they should into the left atrium, and the interauricular septal opening would be closed.

RELATED CASES

Although, as was stated in the introduction, we could find no record of a heart presenting the curious structural and functional conditions here described, there are several cases reported in the literature that involved a similar developmental distortion. The one that seems to come closest to our own case was described by Hosch.[9] His case was that of a 25 day old infant who presented a closely similar clinical picture and fundamentally the same embryologic distortion. There was in Hosch's case, however, an opening through septum primum directly from the accessory median chamber into the left atrium, and consequently there was not the extraordinary circuitous routing of the blood returned from the lungs to the median atrium that was so striking a feature in our case.

Another heart of the same general type, from an infant who lived but a short time, was reported by Stoeber.[10] The accessory median atrium in his case, however, seems to have been a small pocket receiving only the veins from the lower lobes of the lungs. The veins from the upper lobes of both lungs opened into the right atrium, which was in communication with the left, over a widely patent foramen ovale.

Cases involving a similar but less complete division of the primary atrium into three chambers were reported by: Borst[11] (in a woman

9. Hosch, P. H.: Zur Lehre der Missbildungen des linken Vorhofs: II. Ein Herz mit linken Doppelvorhof, Frankfurt. Ztschr. f. Path. **1**:563, 1907.

10. Stoeber, H.: Ein weiter Fall von Cor triatriatum mit eigenartiggekrenzter Mündung der Lungenvenen, Virchows Arch. f. path. Anat. **193**:252, 1908.

11. Borst, M.: Ein cor triatriatum, Verhandl. d. deutsch. path. Gesellsch. **8**:178, 1905.

aged 38); Church [12] (in a woman aged 38, mother of four children); Potter and Ranson [13] (in an "adult" male negro); and William and Abrikossoff [14] (in a boy aged 11).[2] With the exception of Church, whose paper antedates the fundamental work of Born [8] and Tandler [15] on which the present conception of heart development is based, these authorities are in fair agreement regarding the accessory septum as a displaced septum primum, although their conjectures as to the manner and cause of its displacement vary considerably.

Other cases involving what was described as a partial subdivision of the left atrium by a "fibrous band" have been reported by: Griffith [16] (two cases), Fowler [17] and Martin.[18] Probably also Preisz' [19] cases 13 and 14 should be included in this group.[20] It is difficult to be certain without an opportunity of studying the actual specimens, but all these cases of a fibrous band across the left atrium would seem to be instances of a septum primum displaced to the left. If this interpretation is correct, these hearts belong in the same general category embryologically as the true triatrial hearts, for they exhibit the same malposition of the same septum, differing only in that the septum is meager in extent.

Clinically, of course, the cases with a mere fibrous band presented a picture different from the cases in which there was an almost completely isolated accessory chamber. They gave little or no manifestation of cardiac disturbance, and the existence of any malformation was

12. Church, W. S.: Congenital Malformation of Heart: Abnormal Septum in Left Auricle, Tr. Path. Soc. London **19**:188, 1868.

13. Potter, P., and Ranson, S. W.: A Heart Presenting a Septum Across the Left Auricle, J. Anat. & Physiol. **39**:69, 1904.

14. William, N., and Abrikossoff, A.: Ein Herz mit linkem Doppelvorhofe, Virchows Arch. f. path. Anat. **203**:404, 1911.

15. Tandler, J.: The Development of the Heart, in Keibel and Mall: Manual of Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 534.

16. Griffith, T. W.: Heart with a Fibro-Muscular Band Passing Across the Cavity of the Left Auricle, J. Anat. & Physiol., 1896, vol. 30, Proceedings, p. 6; Note on a Second Case of a Division of the Cavity of the Auricles into Two Compartments by a Fibrous Band, ibid. **37**:255, 1903.

17. Fowler, J. K.: Membranous Band in the Left Auricle, Tr. Path. Soc. London **33**:77, 1882.

18. Martin, S.: A Heart with Left Auricle Divided by a Septum, J. Anat. & Physiol., 1899, vol. 33, Proceedings, p. 31.

19. Preisz, H.: Beiträge zur Lehre von den angebornen Hertzanomalien, Beitr. z. path. Anat. u. z. allg. Path. **7**:245, 1890.

20. The case of triatrial heart reported by Sternberg (Beiträge zur Herzpathologie, Verhandl. d. XIV deutsche path. Gesellsch. 1913, p. 253) appears to belong in a totally different category. He described it as having a double right atrium. From his description it would seem that the anomaly might be due rather to persistence of a strongly developed septum spurium than to malposition of septum secundum as he suggests. In any event, the septum primum was not involved as was the case with the heart under consideration.

unsuspected till discovered at the autopsy table or in the dissecting room. Taken as a group, the cases in which the septum is strongly developed show an increase in the severity of symptoms and a decreased tenure of life proportional to the completeness with which the displaced septum primum shuts off from the left atrium, the blood returned from the lungs to the median atrium.

THE FORMATION OF HYALIN IN THE OVARIES*

M. A. GOLDZIEHER, M.D.
AND
IRVING SHERMAN, M.D.
BROOKLYN

Hyaline substances in the ovary are common. Most of this hyalin appears in the form of bulky hyaline masses which are usually interpreted as results of the involution of lutein bodies. Other smaller hyaline bodies are derived from the involution of atretic ovarian follicles. In reviewing the literature, we find that no other form of hyalinization is mentioned, and the foregoing interpretation of the hyaline bodies is given also by all the textbooks of pathology.

Boeshagen [1] distinguished various kinds of hyalin and mentioned the following four types as the most important:

1. The corpus atreticum. This is a small body, round or oval of shape. Its center consists of fibrous or slightly myxomatous tissue, while the periphery appears sometimes as a homogeneous hyaline seam.

2. The corpus fibrosum. This is larger. It consists of irregularly outlined and more or less thoroughly hyalinized fibrous tissue. There is no hyaline seam in the periphery.

3. The corpus candicans. This is usually elongated and gyrated. Its substance is homogeneous, with the exception that in the center it reveals a small area of fibrillar structure.

4. The corpus albicans. This is much more powerfully developed and consists also mainly of hyalin. There is some fibrillar scar tissue in the center which, although more extensive than in the corpus candicans, is still scanty compared with the surrounding hyaline masses.

Transitions between these four major types are frequent. Boeshagen's interpretation is indicated already by his nomenclature. He assumed that the corpus atreticum develops from degenerating ovarian follicles, whereas the other three types derive from lutein bodies and develop according to the part in which fibrosis or hyalinization occurs in the process of involution.

Observations made on a large number of ovaries which were removed surgically or obtained at autopsy gave us the impression that there are many more sources of hyaline formation. In order to prove this point, systematic studies were made on a series of sixty ovaries.

---

* Submitted for publication, June 19, 1929.

* From the Department of Laboratories, United Israel Zion Hospital.

1. Boeshagen: Ztschr. f. Gynäk. **53**:323, 1904.

Almost every ovary in this series showed the presence of more or less extensive hyalinization; in four only, no hyalin was found. The age of the patient seems to bear no relation to the presence or the extent of the hyalinization. As a matter of fact, large hyaline bodies were present in the ovaries of some of our youngest patients, while there were smaller ones in some of the older patients. The ages of the patients varied from 19 to 53 years.

In studying the regressive changes of lutein bodies, we were impressed by the early invasion of their central portion by connective tissue cells. The proliferation of the latter organizes the hematoma and the necrotic area which are formed in the menstrual body and later also in the lutein body of pregnancy. The peripheral area of the lutein body survives longer, but its final degeneration is inevitable, and the lutein tissue is also replaced by connective tissue. Hyalinization of such scars is a regular feature, but it never goes so far as totally to obscure the fibrillar structure. Boeshagen's description of the corpora fibrosum, candicans and albicans applies fairly well to these bodies, although it is difficult to explain according to his conception why the larger peripheral areas of the corpus albicans and the corpus candicans become so homogeneous. The typical product of the involution of the lutein body is the corpus fibrosum, which is characterized by its irregular elongated, or often stripelike, shape. Another feature of the corpus fibrosum is the presence of pigment, notably hemosiderin, which is seldom missing in its central portion (fig. 1). The pigment is either extracellular or phagocytosed by large cells.

There is no difficulty in recognizing the origin of the corpus atreticum. Rabl, Cohn [2] and particularly Seitz [3] have called attention to regressive changes of the ovarian follicles which do not mature and which degenerate without producing lutein bodies (fig. 2). Still it seems that the cells of the follicular capsule (theca cells) store lipoids and assume a shape resembling that of the lutein cells. They have been spoken of as theca lutein cells and are supposed to proliferate extensively in later pregnancy. Their proliferation, however, has been observed also without pregnancy; probably in connection with menstrual changes. The later fate of these cells has been much discussed. Miller [4] and Wolz [5] held that they degenerate and elicit thereby further changes. The origin of these so-called theca lutein cells has also been questioned. Besides their origin from perifollicular theca cells, an origin from the cells of the ovarian stroma has been claimed for them, particularly by Benthin.[6] He also claimed that these cells, after dis-

2. Cohn: Arch. f. Gynäk. **77**:367, 1909.
3. Seitz: Zentralbl. f. Gynäk. **29**:257, 1905.
4. Miller: Arch. f. Gynäk. **91**:263, 1910.
5. Wolz: Arch. f. Gynäk. **97**:131, 1912.
6. Benthin: Arch. f. Gynäk. **91**:498, 1910.

posing of the stored up lipoids, are capable of reverting to their original type, assuming the shape of ordinary stroma cells. According to this conception, the so-called vegetation of the lutein cell represents merely a peculiar functional stage of the ordinary ovarian stroma. Benthin's interpretation has been opposed by various observers, especially by Seitz,[3] who claimed that it is easy to show on serial sections a connection between apparently independent groups of lutein cells and atretic follicles. But even Seitz conceded his failure to demonstrate this

Fig. 1.—Involution of lutein body; hyalin in the periphery; fibrotic center; deposit of hemosiderin.

connection in a good many cases. Our own experience has shown that foci of lipoidal cells are often independent from atretic follicles. They occur just as frequently in the deeper medullary portion of the ovary, where follicles are not met with. Transitional forms between ordinary ovarian stroma cells and large lipoid-storing cells are readily observed. We believe that these cells should not be spoken of as lutein cells, since they are different both as to morphology and as to histogenesis from the cells of the lutein body.

The real lutein cell is dense of structure; its cytoplasm is definitely eosinophile, with the exception of a few scattered cells conspicuous for their basophile cell body. Fat-storing cells of the ovarian stroma, on

the other hand, remain practically unstained if hematoxylin eosin is used. Their cytoplasm is foamy and encloses lipoid droplets which are more soluble in alcohol than those of the real lutein cells. The shape of the nuclei is also different. The nucleus of the lutein cell is comparatively large and round and reveals an orderly structure of the chromatin. The nucleus of the stroma cell, on the other hand, is smaller and usually pyknotic. This seems to suffice for distinguishing sharply between these two types of cells. Hence, we shall refer to lipoid-

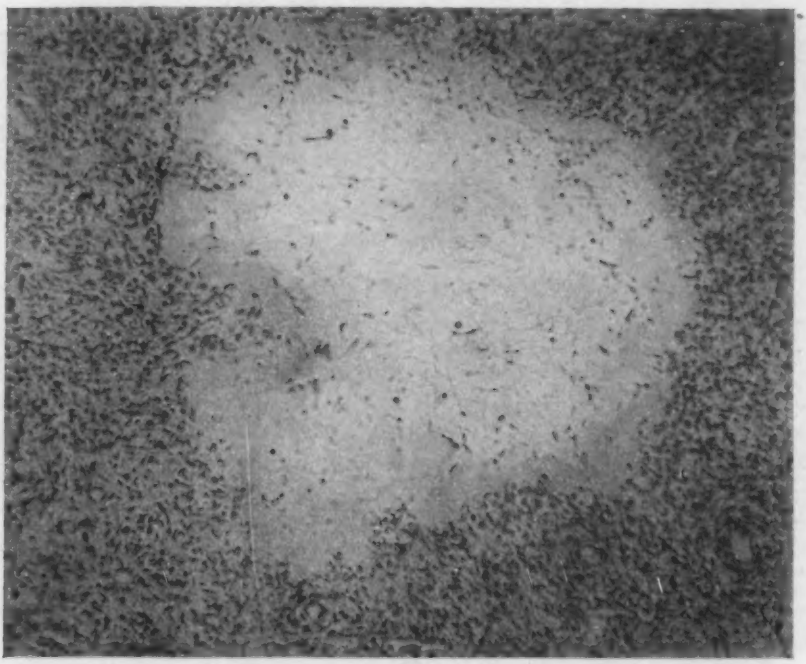


Fig. 2.—Myxomatous focus with hyaline seam; atretic follicle.

storing cells of the ovarian stroma as "lipoidal cells" in contradistinction to the real lutein cells described.

Regressive changes of the lipoidal cells are recognized by the disappearance of the lipoidal material and by subsequent alteration of the cytoplasm. The disappearance of the lipoids is not always followed by injury or death of the cell. The former lipoid cell appears thereafter as an ordinary connective tissue cell or assumes stellate shape and resembles the cells of myxomatous connective tissue. This is apparently due to a collection of fluid in this area. It is in keeping with the fact that the disappearance of fats or lipoids from various tissues is accompanied by a collection of fluid, as, for example, in the cortex of the

suprarenal gland in severe infections (Kutschera-Aichbergen[7]). The myxomatous tissue that forms in the ovary after the resorption of lipoids undergoes sometimes even further changes. Gradual loss of the accumulated fluid transforms the area into plain fibrillar connective tissue in which the cells are small and scanty.

The regressive changes of the lipoid cells, however, are frequently associated with necrotic features. The cytoplasm of the cells becomes homogeneous simultaneously with the resorption of the lipoids. Exudation of an albuminous substance between the cells is concomitant. First,

Fig. 3.—Hyaline degeneration of lipoidal cells in ovarian stroma.

the outlines of the cell bodies disappear, and the nuclei succumb to chromatolysis. Finally, the whole area is transformed into a hyaline mass.

The sources of hyalin in the ovary are not exhausted by the regressive changes of lutein bodies and the vegetations of lipoid cells, or by those of the atretic follicles. Independently from such structures, hyaline material is directly formed in the ovarian stroma. The final product of hyalinization in the ovarian stroma is not easily distinguished from hyalin that derives from any of the sources mentioned. The early stages, however, are characteristic. At the onset, minute deposits

7. Kutschera-Aichbergen: Verhandl. d. deutsch. path. Gesellsch. **20**:133, 1925.

of hyalin of annular shape surround the single stroma cell. While this ring of hyalin becomes more massive, the stroma cell shows evidence of progressing atrophy with the result that a small spindle-shaped nucleus is left in the center of a lump of hyalin. Isolated hyaline rings of this type are rare. Hyalin develops usually about a whole group of cells. Many of these rings coalesce and form wavy, garland-shaped structures (fig. 4). The process resembles closely hyalinization in a lymph node or a deposit of amyloid. The reaction of the ovarian stroma cells to the presence of hyalin is similar; atrophy of cells is followed

Fig. 4.—Formation of hyalin in the ovarian stroma.

sooner or later by complete disappearance of the nuclei; finally the hyalin coalesces to form solid masses of gyrated shape (fig. 5).

Hyalinization of the ovarian stroma of the type described occurs both in the cortex of the ovary and in the stroma of the medulla. These deposits of hyalin are sometimes insignificant, but they may involve also a large portion of the ovary. Careful review of our material leads us to the conclusion that most of the hyaline bodies and particularly the large ones derive from direct changes in the ovarian stroma.

Another group of hyaline changes includes those developing in the walls of blood vessels. Hyalin is frequently deposited in the wall of the small and medium-sized arteries or veins. Most of this hyalin occurs in the media, but deposits are found also in the intima and the

adventitia. The specific elements of the musculature disappear with increasing hyalinization, while the lumen of the vessel is often narrowed down considerably. Complete obliteration of the blood vessel is the final stage. This is brought about by homogeneization of the vessel wall and coalescence of its structures into a solid hyaline, disklike body. Vessels with such extensive hyalinization usually occur in densely packed groups (fig. 6). If the adventitia is also involved, as often happens, some of these vessels fuse, forming a large hyaline body. This body is oval and elongated, and its gyration resembles that of the hyaline

Fig. 5.—Coalescing hyaline garlands.

structures formed within the ovarian stroma. It is almost impossible to distinguish these late stages of vascular degeneration from other products of hyalinization. Residua of the original structure persist sometimes and reveal the histogenesis. Earlier stages of such vascular changes in the vicinity of hyaline bodies can be considered as further circumstantial evidence.

Severe impairment of the ovarian blood vessels, particularly in the medulla, has been discussed previously by several authors (Sohma,[8] Miller,[4] Clark[9]). Their interpretation is that the lesion develops in

8. Sohma: Arch. f. Gynäk. **84**:377, 1908.
9. Clark: Surg. Gynec. Obst. **13**:99, 1911.

connection with disturbances during pregnancy. Other authors thought that these changes might result from the strain to which the ovarian vessels are subjected during menstruation. Neither of these theories has been sufficiently substantiated. Yet it is fair to say that the vascular changes are not in proportion to the age of the person and cannot be explained simply as products of senile involution.

SUMMARY AND COMMENT

We have distinguished in the foregoing description between various types of hyalinization in the ovary. Our differentiation is based on the

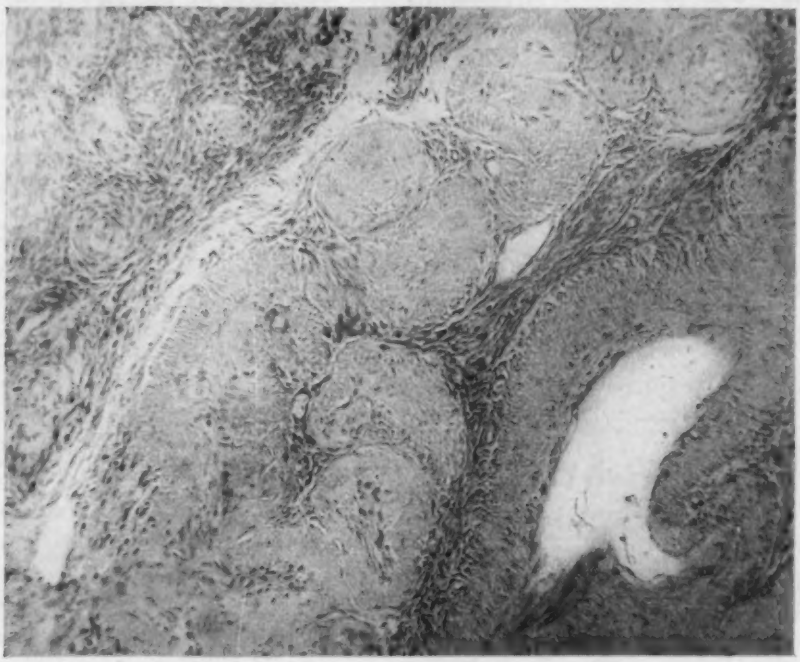


Fig. 6.—Hyalinization of ovarian blood vessels.

morphologic appearance of the hyaline bodies. Yet it also takes into consideration their histogenesis as brought out by comparing earlier and later stages. Summarizing briefly, we may state that there are five types of hyaline bodies in the ovary. The first derives from lutein bodies and is fairly well characterized by its scarring center and the presence of hemosiderin. The second type is a small hyaline body developing from an atretic follicle through degeneration of theca lipoid cells. The third type develops from lipoid cells that were formed in the ovarian stroma independently from any follicle. Degeneration of such lipoid cells yields a colorful picture as myxomatous or plain

fibrous areas intermingle. The fourth type develops directly within the specific ovarian stroma and represents a primary lesion of the stroma cells. The fifth group is the result of changes to which the ovarian blood vessels were subjected.

We have to emphasize that in their fully developed stage, all the different types of hyaline bodies may look so similar that histogenetic differentiation is not possible. Differential diagnosis can be made only in the early stages. But even then difficulties may arise in that several types occur simultaneously and combine to form puzzling structures. The most common combination is a deposit of hyalin in the ovarian stroma adjacent to a hyalinized lutein body. It is not rare to find vegetations of lipoidal cells near, or surrounding, a comparatively recently involuted lutein body. Coalescence of the two different structures forms a large body, the core of which represents the residua of the lutein body, and the periphery, the degenerated lipoidal cells. The distribution of the hyalin may be annular or crescent-like. Hyalinized blood vessels may also participate in the formation of a homogeneous marginal zone about an involuted lutein body. Hyalinized blood vessels, however, coalesce more frequently with masses of hyalin formed directly in the ovarian stroma.

We do not know the real significance of hyalinization in the ovary. We could not by comparing establish any definite relationship between the age of the patient and the extent of the changes. The presence of extensive lesions in young persons seemed to prove that hyalinization in the ovary is not connected with senile involution. We tried to determine in our surgical cases whether any coincidence obtained between ovarian hyalinization and disturbances of menstruation. We were unable to find any convincing evidence of this. However, most of our material was obtained from patients on whom operations had been performed for some disturbance of the genital sphere. Therefore, this material does not seem to be suitable for deciding on the relationship of ovarian hyalinization to clinical symptoms. It would be necessary to study an equal number of ovaries from patients who were without any disturbance of the genital organs.

CONCLUSIONS

Hyalinization of the ovary was studied in sixty ovaries. Five types of hyaline bodies were described. They derive from lutein bodies, from atretic follicles, from lipoidal cells of the ovarian stroma, from ordinary stroma cells and from blood vessels, respectively. The histogenesis of a hyaline body can be distinguished only in the early stage of its formation. Combination forms are common.

The clinical significance of ovarian hyalinization requires further comparative studies.

HEMANGIOBLASTOMA OF THE CEREBELLUM WITH CYST FORMATION (LINDAU'S DISEASE)

REPORT OF A CASE *

PHILLIP SHAPIRO, M.D.
CHICAGO

Cysts comprise about 10 per cent of all cerebellar tumors. It has long been recognized that some of them arise by cystic degeneration of gliomas. The remainder are grouped as nonneoplastic or simple cysts. It was only three years ago, in 1926, that Lindau [1] expounded the origin of many of these so-called simple cysts from small hemangiomas which can be readily found by close inspection of the wall of the cyst. He indicated the heredofamilial character of hemangiomatous cysts, and pointed out also their frequent association with angiomatosis of the retina (von Hippel's disease) or with other visceral tumors. Cushing and Bailey [2] brought his work closer to date, and lent to it special staining analyses. Davidoff [3] recently reported a case of this newly established syndrome.

Altogether, less than sixty cerebellar hemangiomas with cyst formation and companion tumor have been described.[4] Postmortem examination disclosed another one to me. The relatively recent establishment of the syndrome, its infrequency and an unusual feature in my case make the latter worthy of being reported.

REPORT OF CASE

Clinical History.—A male mulatto, about 50 years old, entered the Cook County Hospital. He was apparently well until three months before entrance when he became rapidly weak in the right side of the body and the right arm began to tremble. He managed to carry on for two months longer; then mental deteriora-

* Submitted for publication, July 3, 1929.

* From the Department of Pathology of the Cook County Hospital.

1. Lindau, Arvid: Studien über Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, suppl. no. 1, pp. 1-128.

2. Cushing, H., and Bailey, P.: Tumors of the Brain Arising from Its Blood Vessels, Springfield, Ill., Charles C. Thomas.

3. Davidoff, L. M.: Hemangioblastoma of the Cerebellum (Lindau), Am. J. Path. **5**:141 (March) 1929.

4. After our paper was submitted for publication, an article appeared by Sargent and Greenfield (Hemangiomatous Cysts of the Cerebellum, Brit. J. Surg. **17**:84 [July] 1929), reporting a collection of nine cerebellar cysts. In seven of these, angiomas were found. In several cases, a severe trauma to the head was associated. The authors suggest that the trauma may have started the formation of a cyst in a patient who already had an angioma of the cerebellum.

tion set in. It progressed so rapidly that within a month he was practically vegetative. Such was his apathy that from time to time he had to be fed by means of a tube until he could collect himself sufficiently to swallow food of his own accord.

Neurologic examination revealed a spontaneous lateral nystagmus of the eyes, an intention tremor of the right hand and weakness in both lower extremities. There were increased patellar reflexes and an absence of abdominal reflexes. The coordination in both upper extremities was impaired. The Wassermann reactions of the blood and the spinal fluid were negative. Emaciated, volitionless, stuporous, he finally died of a hypostatic bronchopneumonia.

Postmortem Observations.—The essential changes were in the brain and the kidney.

Brain: The cerebral convolutions were rather deep, and a moderate amount of fluid filled the sulci. The lateral ventricles were but slightly distended with fluid. On the superior aspect of the right hemisphere, the cerebellar tissue over

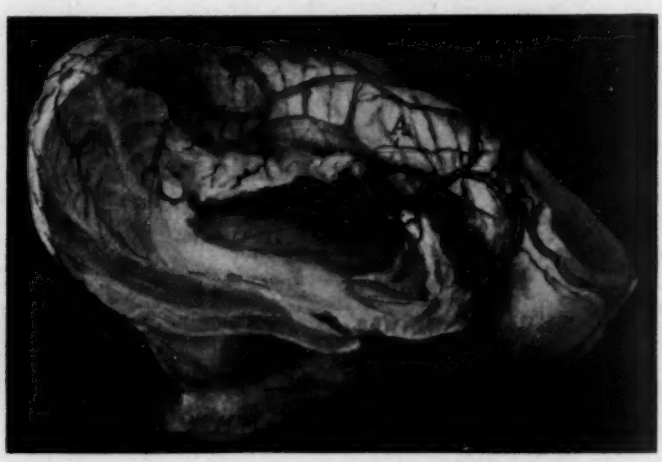


Fig. 1.—A drawing made from the gross specimen, with longitudinal section through the right cerebellar hemisphere, showing the collapsed cyst with its mural tumor (*A*), and its relation to the cortical vessels.

an area 5 by 4 cm. was collapsed to 2 cm. below the surface. In the lateral portion of this depressed area, broadly bridging two of the posterior superior cerebellar vessels, was a deep purple, soft, round mass, the size of a pea, slightly elevated above the surface. Longitudinal section disclosed the right hemisphere, under the depressed area described, to be the site of a large cyst (fig. 1). The cyst attained a size of 4 cm. in the longitudinal, and 3 cm. in the transverse diameter, and 2 cm. in its collapsed height. Its roof was thin; in places, transparent. The mass described was 3.5 cm. thick; it extended through the whole roof of the cyst and bulged into its cavity. On the cut surface, it was reddish purple. The floor of the cyst was lost in broad communication with the fourth ventricle.

Microscopically, the purple nodule on the superior aspect of the cyst was composed of numerous wide, capillary blood spaces, lined by a distinct endothelium (fig. 2). Most of these spaces were filled with blood; some contained only a pale pink, homogeneous, plasmatic material. Fine capillaries could also be dis-

tinguished, with all transitions between them and the larger blood spaces. The intervening, loose fibrillar tissue was occupied by cells which contained each a large, pale, oval or slightly indented nucleus with an ample cytoplasm (fig. 3). Sudan III stain revealed these cells to be filled with lipoid. There were aiso single round cells with deeply stained nuclei and homogeneous cytoplasm. The rest of the wall of the cyst was composed of cerebellar tissue which formed a lining layer, rich in glia, and which continued for but a short distance over the inner aspect of the angiomatous area.

Kidney: A 5 mm. white nodule at the corticomedullary line was seen microscopically to be composed of long, narrow and branched tubules lined by irregular cuboidal epithelium with rather pale, round or oval nuclei (fig. 4). The tubules were separated from one another by thin septums, and were divided

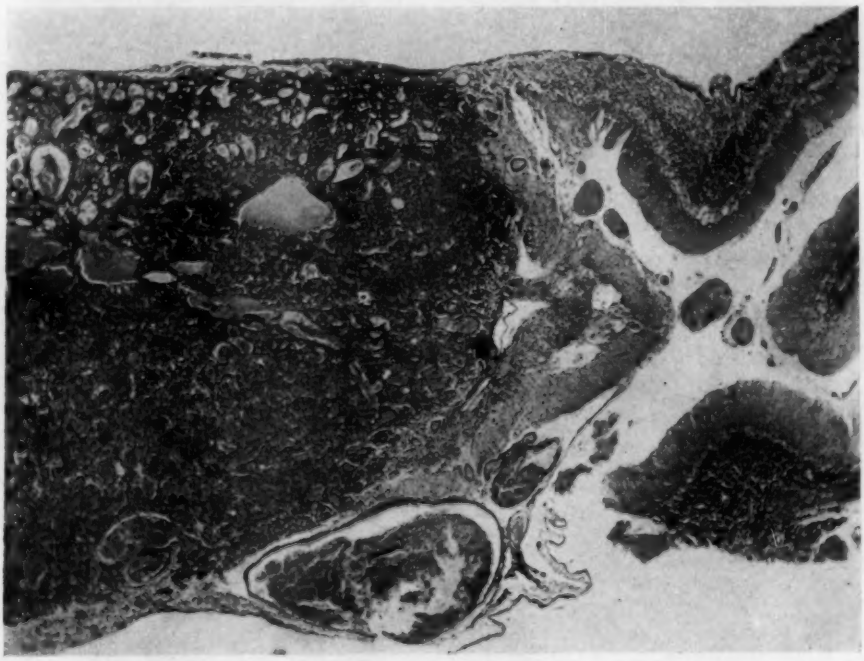


Fig. 2.—Low power view of the hemangioma in the roof of the cyst with the adjacent cerebellar tissue lining the rest of the cyst wall; × 28.

into groups by thicker strands of fibrillar connective tissue. The nodule was sharply circumscribed but not encapsulated, and a few of its tubules were found outside among the normal ones.

Pathologic Diagnosis.—The pathologic diagnosis was: hemangioblastoma of the right cerebellar hemisphere, with cyst formation, the latter communicating with the fourth ventricle (Lindau's disease); adenoma of the kidney; confluent bronchopneumonia of the left lower lobe; edema and hyperemia of the lungs; atrophy and inflammatory softening of the spleen; brown atrophy and cloudy swelling of the myocardium and liver; cloudy swelling and passive congestion of the kidneys, and healed tuberculous primary nodule in the right lower pulmonary lobe.

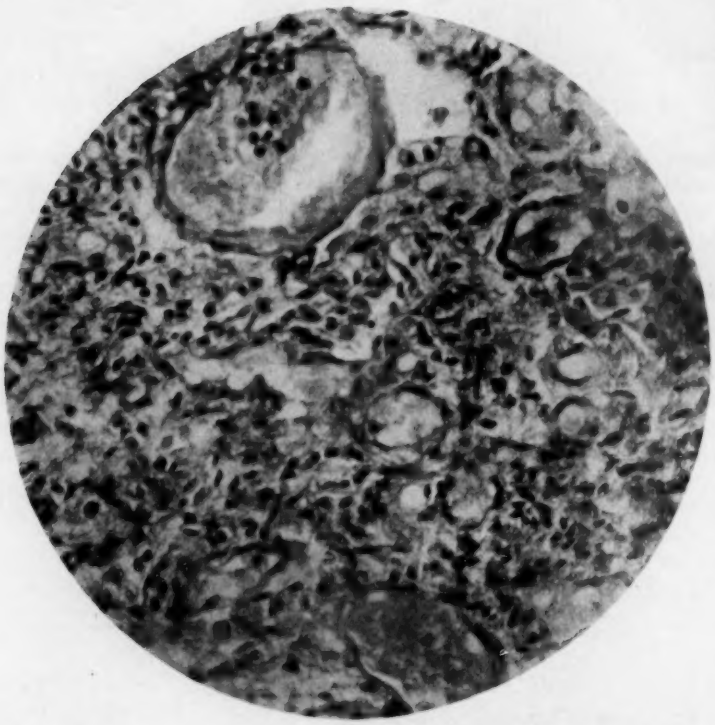


Fig. 3.—High power view of the capillary and cavernous hemangioma. The large, pale nuclei in the stroma belong to the "pseudoxanthoma" cells with their fat-laden, vacuolar cytoplasm; × 250.

Fig. 4.—Low power view of the renal adenoma (on the right) sharply defined from the normal kidney tissue (on the left); × 70.

COMMENT

The writings of Lindau [5] and of Cushing and Bailey [6] leave little which my work can add to the knowledge of cerebellar hemangioblastomas. Their origin is ascribed to the vascular mesenchyme in the roof of the fourth ventricle. These neoplasms are practically confined to the cerebellum, medulla and cord, in distinction from angioma-like, congenital vascular malformations which are similarly confined to the cerebrum. Cellular, capillary or cavernous structure may predominate. They tend to become cystic, but may be solid, and all gradations exist between.

The cyst formation is held usually to be not the result of degenerative changes in the tumor, but the result of an active transudation arising from circulatory disturbances in its young vessels. This transudation may attain high pressure, and then causes necrosis of the adjacent brain tissue. Within the mural tumor, the scavenging, "pseudoxanthoma," fat-laden cells of the stroma absorb the necrotic brain substance.

No angiomatous cyst, large as the necrosis caused by its pressure may have made it, has ever been described as opening into the fourth ventricle. Simple cysts without angioma have been so described, and are regarded as developmental defects in the cerebellum. Our case is unique, therefore, in that it is the first hemangiomatous cyst reported which had a communication with the fourth ventricle. Two mechanisms may here have been in operation. The pressure by the angiomatous transudation may by necrosis of tissue have produced a larger and larger cyst in the cerebellar substance, until it finally ruptured into the fourth ventricle. Or else the disturbance of the growth of the blood vessel associated with the tumor may have determined, by deficiency of blood supply, a localized defect in cerebellar development. Whether the factor of necrosis from pressure or that of developmental defect here predominated is uncertain.

Lindau, and all investigators of this syndrome after him, emphasized the association of cerebellar hemangiomas with benign tumors in other parts of the body, and particularly its association with angiomatosis of the retina. He compared it to tuberous cerebral sclerosis, von Recklinghausen's disease and other heredofamilial syndromes, in which some external manifestation guides the diagnosis of the internal ones. The cerebellar hemangioma may find its associated tumor in the spinal cord, the pancreas, the liver, the kidneys, the suprarenal glands, the urinary bladder, the epididymis or the bones. The associated tumor

5. Lindau, Arvid: Zur Frage der Angiomatosis retinae und ihrer Hirnkomplikationen, Acta ophth. **4**:193, 1927.

6. Cushing, H., and Bailey, P.: Hemangiomas of the Cerebellum and Retina (Lindau's Disease), Arch. Ophth. **57**:447 (Sept.) 1928.

in my case was a renal adenoma. Often, however, the only external sign for antemortem diagnosis is an angiomatosis of the retina (von Hippel's disease). This well recognized condition presents to the ophthalmoscope a dilated tortuous vein and a beaded artery which lead together to an angiomatous nodule somewhere in the fundus. At times this nodule may be close to the disk, but usually it is far in the periphery, so that its detection necessitates examination under a well dilated pupil.

Not always are they correlated, but if a case of von Hippel's disease is found it should be watched for the development of intracranial complications. What is even more important is that with a diagnosis of cerebellar tumor, the finding of a retinal angiomatosis establishes this tumor as an angioma. In my case, the fundi were not examined clinically. I regret that no permission could be obtained for post-mortem examination of the eyeballs. I take this occasion to reiterate Lindau's and Bailey's emphasis on the importance of examining the fundi for angiomatosis. Only by its presence can one, before operation or autopsy, distinguish between angioma and all other cerebellar tumors.

The reward of the diagnosis lies in the especially favorable surgical prospects. Practically no other cerebellar tumor gives such gratifying surgical results as does the angioma. Simple puncture of the cyst may relieve the condition for several years, while enucleation of the angioma gives permanent cure.

SUMMARY

A case of hemangioblastoma of the cerebellum (Lindau's disease) with formation of a cyst, unique in its broad communication with the fourth ventricle, is reported. It was accompanied by a renal adenoma. The importance of angiomatosis of the retina as a diagnostic aid in distinguishing cerebellar angioma is emphasized.

STUDIES ON THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS *

KURT SEMSROTH, M.D.
AND
ROBERT KOCH, M.D.
PITTSBURGH

In view of the well known multiplicity of bacteria isolated from endocarditic lesions, workers in this field have always more or less distinctly felt that the essential question in the pathogenesis of endocarditis is one of bacterial localization. Under what conditions will bacteria localize on the endocardium? While early experimental investigators (Wyssokowitsch,[1] Ribbert[2]) succeeded in producing endocarditis by combining the bacterial infection with a gross trauma to the heart valves, observations on experimental endocarditis without such trauma (Lissauer,[3] Saltykow[4]) have been rare until recently. Wadsworth[5] pointed out the relatively frequent development of fatal endocarditis in horses which had received repeated injections of killed and living pneumococci for the purpose of immunization. In this case, the preceding application of killed pneumococci appears to be the determining factor for bacterial localization on the endocardium.

Birkhaug[6] produced a subcutaneous focus of streptococci in rabbits with infected agar and induced endocarditis regularly by a single intravenous reinjection of the organism. As the regular production of endocarditis by a single injection of streptococci or other micro-organism has not been possible thus far, one has to infer that in Birkhaug's work the essential condition for the bacterial localization on the endocardium was the preceding establishment of a subcutaneous focus of streptococci.

---

* Submitted for publication, Aug. 24, 1929.

* From the Western Pennsylvania Hospital Institute of Pathology, Dr. Ralph R. Mellon, Director.

1. Wyssokowitsch: Virchows Arch. f. path. Anat. **103**:307, 1886, reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

2. Ribbert: Fortschr. d. Med. **4**:1, 1886.

3. Lissauer: Centralbl. f. allg. Path. u. path. Anat., 1912, vol. 23, no. 6; reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

4. Saltykow: Virchows Arch. f. path. Anat. **209**:126, 1912; reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

5. Wadsworth: J. M. Research **39**:279, 1918-1919.

6. Birkhaug: J. Infect. Dis. **40**:549, 1927.

That no relationship between this "determining factor" and the subsequent infection in the sense of specificity needs to exist was apparent in Freifeld's work.[7] She obtained endocarditis in rabbits with considerable regularity by repeated injections of killed streptococci and subsequent infection with staphylococci.

Kuczynski,[8] working on mice, injected from 0.3 to 0.5 cc. of a culture of *Streptococcus viridans* intravenously from eight to sixteen times. He frequently observed subendocardial proliferations of "typical plasma cells," comparing them with early manifestations of endocarditis in man. He did not, however, obtain processes that went beyond this proliferative stage. Silberberg,[9] in his work on the behavior of the "vitally stored" body against septic general infection, gave rabbits six successive daily injections of Aschoff-Kiyono's lithium carmine solution. On subsequent intravenous infection with *Staphylococcus* all the five animals employed developed endocarditis. In this case, the determining factor for bacterial localization on the endocardium was evidently the preceding application of lithium carmine. Siegmund[10] produced experimental endocarditis in rabbits by daily intravenous injections of rapidly increasing doses of *Bacillus coli* or *Staphylococcus.* Siegmund and Dietrich[11] concluded that a peculiar state of immunity, associated with an altered capacity of the endocardium to react, is the essential condition for bacterial localization on the endocardium.

Alteration of the reactivity of a host against a subsequent infection is the object of a study which we started some time ago with observations on the influence of immunobiologic processes on the course of subsequent general infections.

EXPERIMENTS

Guinea-pigs were sensitized by one intraperitoneal dose of 0.5 or 2 cc. of horse serum. After skin hypersensitivity was apparent (eighth to eighteenth day), the animals were infected intraperitoneally with varying doses of paratyphoid bacilli or staphylococci. With considerable regularity, an endocardial lesion developed in the sensitized guinea-pigs; this was only occasionally met with in nonsensitized controls. The lesion consisted of nodular or plateau-like mononuclear cell proliferations with occasional karyorrhexis, a process which in human pathology has been termed proliferative endocarditis.

As a sequel of sensitization to horse serum, the capacity of the endocardium to react against an infection has evidently been altered.

7. Freifeld: Klin. Wchnschr. **7**:1645, 1928.
8. Kuczynski: Verhandl. d. deutsch. path. Gesellsch. **18**:47, 1921.
9. Silberberg: Virchows Arch. f. path. Anat. **267**:483, 1928.
10. Siegmund: Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923.
11. Dietrich: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **27**:188, 1925.

Has this altered capacity of the endocardium to react any bearing, and in what way, on the problem of the pathogenesis of human endocarditis?

In human endocarditis, the earliest endocardial change has, until recently, generally been supposed to be an "endothelial damage" preceding the localization of bacteria. This endothelial damage has never, however, actually been observed.

Mononuclear endocardial cell proliferations, on the other hand, are a well known constituent of the picture of human endocarditis. Ribbert, presenting the histology of endocarditis verrucosa (1924), referred to endocardial proliferations of large polyhedral elements as present underneath the thrombotic deposits and extending to some extent underneath the adjoining intact endocardial surface. In his presentation there is little if any doubt about the sequel of events: a hypothetic endothelial damage leads to localization of bacteria and formation of thrombotic deposits. The thrombotic masses penetrate into the valvular tissue, leading to the appearance of broad homogeneous bands. Subsequently, a secondary proliferation of large polyhedral cellular elements sets in. Although penetrating thrombotic deposits are, as he stated, hardly ever seen without the aforementioned proliferative changes, Ribbert did not seem to doubt seriously that thrombi regularly precede the cellular proliferations. Patients, he argued, do not die at a stage when the thrombi have not yet been followed by proliferative changes, and therefore one has no chance to observe these earliest stages. In this, thus far dominant, interpretation, primary endothelial damage, as well as the penetration of thrombotic masses into the tissue, remains a logical requirement of the theory, though not wholly founded on actual observations.

Autopsies on several patients who showed early endocarditis have furnished us the possibility of studying early endocardial reactions in endocarditis. In these patients, nodular monocytic proliferations were not infrequently observed underneath an intact endothelium and far from the site of thrombotic deposits (fig. 1). This observation allows the conclusion that monocytic endocardial proliferations in human endocarditis are not invariably the sequel of thrombotic deposits.

Furthermore, in several mononuclear endocardial cell proliferations, areas of transformation of the intercellular substance into hyalin were found associated with a defect of the surface endothelium, but without a thrombotic deposit. We infer, then, that in human endocarditis not only may mononuclear cell endocardial proliferations arise in the absence of thrombotic deposits, but, on the other hand, they may, through regressive changes, develop endocardial defects which in turn may become the site of thrombi.

In other words, nodular mononuclear cell proliferations of the human endocardium may precede the formation of morphologically

detectable endocardial defects and endocardial thrombotic deposits; i. e., they are one of the earliest endocardial reactions in human endocarditis.

Do identical considerations prevail in the experimental animal endocarditis? In order to approach the latter question, an endocarditis was induced in rabbits by intravenous streptococcic vaccination and subsequent infection with staphylococci (after Freifeld). It was found that the endocarditic nodule of such a rabbit consisted of large mononuclear cellular elements. Near the free surface, degenerative changes and superficial accumulation of cocci were noted. The picture has to be interpreted as a mononuclear cell proliferation followed—not preceded—by the formation of thrombotic deposits.

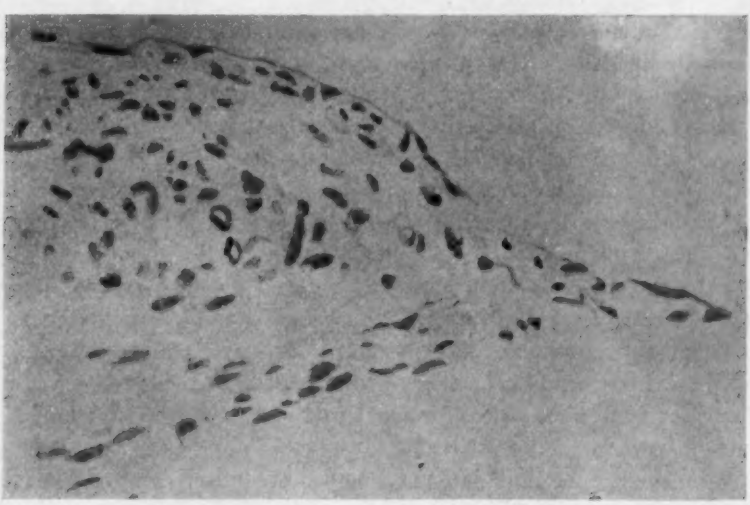


Fig. 1.—Human rheumatic endocarditis: nodular endocardial proliferation. One may note marked polymorphism of proliferating elements; lack of polarity; absence of definite endothelial defect and absence of thrombosis. (Zeiss, Abbe drawing apparatus; actual magnification 400 ×.)

It is seen, then, that in human endocarditis, as well as in experimental rabbit endocarditis, nodular mononuclear cell proliferations represent the earliest endocardial reactions and are analogous to the endocardial reaction of the guinea-pig that has been sensitized to horse serum and subsequently infected. Are we therefore to infer that processes somehow related to that of sensitization to horse serum are one essential condition for bacterial localization on the endocardium?

In an effort to answer this question, various measures were tried to induce a true endocarditis in guinea-pigs and rabbits.

1. Intraperitoneal paratyphoid, as well a staphylococcus, infection of guinea-pigs senstized to horse serum led to the nodular reaction of the

endocardium, but never to a true endocarditis. Desensitization after the infection did not alter the result. Desensitization before the infection practically prevented the nodular endocardial reaction. These experiences confirmed our assumption of a relationship between endocardial reaction and hypersensitiveness, but failed to furnish information as to the rôle of that reaction in the genesis of true endocarditis.

Production of Endocarditis in Rabbits by Infection with Staphylococcus Following a Course of Intravenous Casein Injections

Day of Experiment	Rabbits							
	J_3	J_4	J_6	J_7	J_8	X_1	X_2	X_4
1	Received 5 daily casein injections	Received 5 daily casein injections	Received 10 daily casein injections	Received 10 daily casein injections	Received 10 daily casein injections	Received 10 daily casein injections	Received 10 daily casein injections	Received 10 daily casein injections
2								
3								
4								
5								
6	Received 1.5 cc. staphylococci intravenously	Received 2 cc. of staphylococci intravenously						
8	Died							
9	.....	Died						
10								
11	.....	.....	Received 1.5 cc. staphylococci intravenously	Received 1.75 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 1 cc. staphylococci intravenously
14	.....	.....	.....	.....	Died	2 cc. staphylococci intravenously	2 cc. staphylococci intravenously	2 cc. staphylococci intravenously
16	.....	.....	.....	.....	.....	Died		
22	.....	.....	.....	.....	.....	.....	Died	
23	.....	.....	Killed	Killed				
28	.....	.....	.....	.....	.....	.....	.....	Killed
Postmortem blood culture	Staphylococci aureus	Staphylococci aureus	Negative	Staphylococci aureus	Staphylococci aureus	Staphylococci aureus	Negative	Negative
Endocarditis	Negative	Positive	Negative	Positive	Positive	Positive	Positive	Positive

2. Guinea-pigs received five successive intraperitoneal doses of 2 cc. of polyvalent streptococcic vaccine. On subsequent intraperitoneal paratyphoid infection, one of five animals presented a marked endocardial lesion. The latter was characterized by nodular monocytic proliferations with superficial defects, beginning thrombus formation and degeneration of adjoining muscular elements—a picture which was interpreted as an early endocarditis. The remaining four showed only the nodular endocardial reaction.

3. In a third series, a nonbacterial foreign protein was substituted for the bacterial vaccine. Rabbits received either five or ten successive daily intravenous doses of 2 cc. of 2 per cent casein in 0.1 per cent sodium carbonate. After from five to ten injections, ten of fifteen animals showed at the site of the injection of the casein, a definite, and five, a less definite, allergic skin reaction characterized by a predominance of eosinophils in the resulting abscess. Subsequent intravenous infection with varying doses of staphylococci on the sixth or the eleventh day led to a definite endocarditis in six of eight cases. The course of the experiment was, in brief, as set forth in the accompanying table.

In the table, the term "endocarditis" is meant to designate histologic evidences of a primary endocardial localization of bacteria, exclusive of extensions of myocardial foci into the endocardium.

Morphology of the Heart Lesions Induced.—Rabbit J_3.—The animal presented: numerous myocardial abscesses; suppurative pericarditis; nodular proliferation of endothelium in some myocardial veins; exudative periphlebitis of myocardium, and no definite endocardial lesion.

Rabbit J_4.—Rabbit J_4 showed myocardial abscesses and here and there perivascular proliferation of histiocytes. In many instances, the capillary and venous endothelium of the myocardium was covered with masses of gram-positive cocci, which frequently were present also within the cytoplasm of the endothelium. Small endocardial thrombi, largely fibrinous, were found over superficial defects of the endothelial lining, without there being a marked cellular reaction of the underlying structures. Focal plateau-like thickenings of the endocardium through cellular proliferation were seen, with the appearance of intracellular eosinophilic granules outside, as well as within, the continuity of the surface endothelium. Masses of gram-positive cocci were found within the cells of these plateau-like endocardial proliferations. Here and there, a hemorrhagic infiltration of the endocardium was noted.

Rabbit J_6.—Slight interstitial proliferative myocarditis was observed, but no endocardial lesion.

Rabbit J_7.—This rabbit presented no marked myocardial lesion, but focal-nodular or plateau-like-active endocardial proliferations (mitoses). These foci, valvular, as well as parietal, showed intracellular cocci in a few instances. There was no endocardial thrombosis.

Rabbit J_8.—The animal had myocardial abscesses. The changes included: (1) focal thickening of valves through cellular proliferation with the appearance of numerous polymorphonuclear leukocytes, "palisade" orientation of nuclei vertical to the surface, and bacteria within the valvular tissue, but no thrombosis; (2) at other places, similar foci showing extensive surface defects, filled with thrombotic material and masses of bacteria. The latter, in a few instances, were surrounded by large areas of necrosis, giving rise to the picture of an acute ulcerative valvular endocarditis.

Rabbit X_1.—There were myocardial abscesses which, in many instances, were surrounded by zones of muscular calcification. Areas of necrosis were seen with calcification of muscle fibers. The valvular lesions were identical with those in

Rabbit J_8 (1) (fig. 2). There was no thrombosis. Small subendocardial hemorrhages were seen.

Rabbit X_3.—No myocardial lesion was seen. Fibrinous endocardial thrombi were found over superficial defects of the endothelial lining.

Rabbit X_4.—This animal had a slight focal interstitial proliferative myocarditis. At one place, a parietal endocardial "vegetation" was found identical in its histologic structure with the early vegetations in cases of human rheumatic endocarditis. The other changes were a nodular proliferation of large mononuclear tissue elements, cordlike hyalinization of the stroma (Ribbert's "penetrating thrombus") and early surface defect. There was no thrombosis.

Further Observations.—In another group of three rabbits, the intravenous treatment with casein was continued up to twenty days, a total of 60 cc. of the

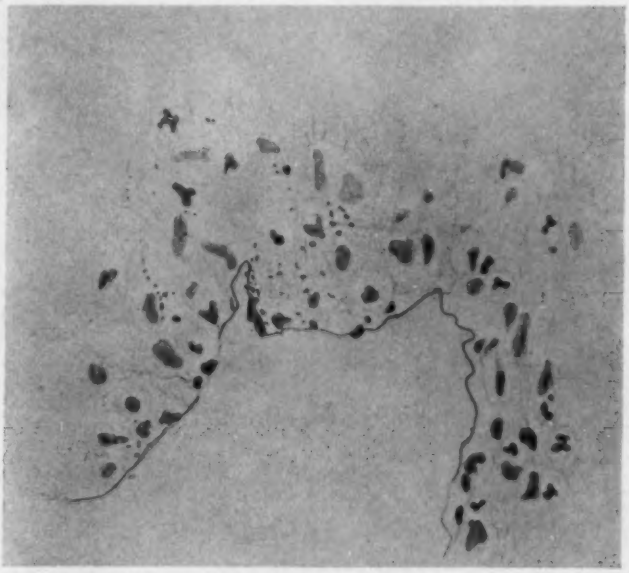


Fig. 2 (rabbit X_1).—Proliferative and suppurative bacterial endocarditis; no definite endothelial defect. (Zeiss, Abbe drawing apparatus; magnification 400 ×).

The rabbit received ten daily casein injections, after which it was intravenously infected with staphylococci. It died two days after the infection.

solution being injected. On the twenty-first day, they received intravenous injections of 2.5 or 3 cc. of a culture of *Staphylococcus aureus*. One animal that died the following day presented fibrinous endocardial thrombi with extensive hemorrhage into the valves. The other two rabbits, which died eight and eighteen days, respectively, after the infection, did not show endocardial lesions and showed negative blood cultures. In four more rabbits the treatment with casein was extended to thirty days, a total of 90 cc. being injected. On the thirty-first day, these animals received intravenous injections of 3, 5, 5 and 10 cc. of a culture of *Staphylococcus aureus*. Three that died the following day presented a suppurative, nonthrombotic endocarditis. One animal that died ten days later yielded a negative blood culture and failed to show endocardial lesions. To summarize:

The extension of the casein treatment over twenty or thirty days did not markedly alter the results obtained in ten days.

Similar results were obtained when the intravenous infection of the animals was delayed until one, two or three weeks after the end of the treatment with casein. Two animals were employed for each stage (fig. 3).

A comparison of the morphologic observations in experimental rabbit endocarditis (figs. 2 and 3) with those in early human endocarditis (fig. 1) leads to the following inference: In the formal genesis of endocarditic lesions, mononuclear cell proliferations may constitute precursors of morphologically detectable endothelial defects.

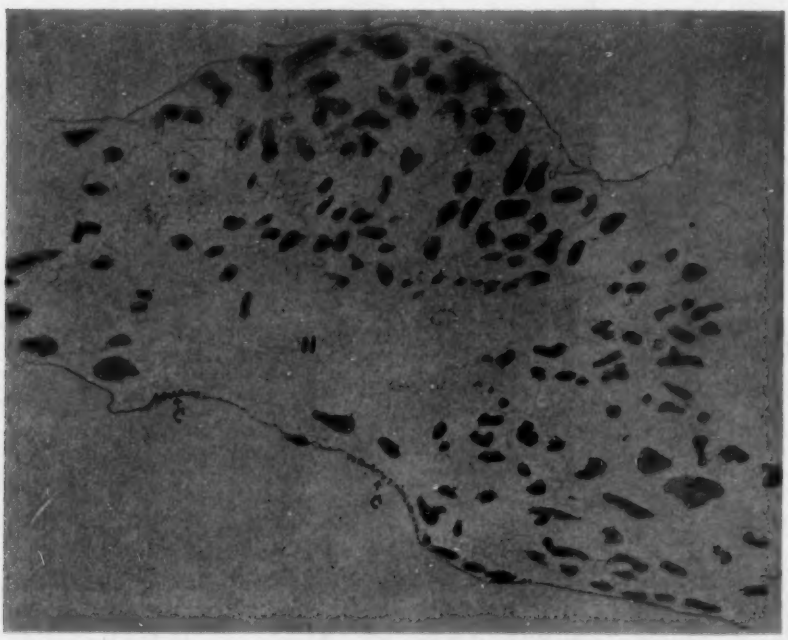


Fig. 3 (rabbit V_9).—Large cell endocardial proliferation; necrosis (*N*); superficial accumulation of cocci (*C*). (Zeiss, Abbe drawing apparatus; magnification 400 ×.)

The rabbit received ten daily casein injections, and seven days after the treatment with casein it was intravenously infected with staphylococci. It died one day after the infection.

Marked breaking down of the histiocytes of the heart valves of rabbits after the latter had received repeated injections of yatren-casein was recently reported by Pfuhl.[12] In four rabbits which had received twenty or thirty daily injections of doses of 2 cc. of 2 per cent casein, we have thus far not been able to corroborate this observation.

12. Pfuhl: Klin. Wchnschr. **8**:1099, 1929.

SUMMARY

It has been possible to modify the course of a staphylococcic bacteremia in rabbits to one characterized by endocarditic lesions. This has been accomplished in two ways: (1) by preceding the infection with staphylococci by intravenous injection of killed streptococci; (2) by preceding it by intravenous injections of casein. Although the treatment with casein, per se, has never led to morphologically detectable cellular damage, it has been a prerequisite for the development of bacterial endocarditis.

The inference that bacterial localization on the endocardium results from its altered capacity to react toward bacteria would seem logical. This relationship, however, is scarcely true within the confines of specificity, as the "allergic state," so-called, may be induced by a non-bacterial, foreign protein. It remains a matter of further study to what extent, and how, the "allergic state" referred to may be correlated with definable alterations of cellular activity.

THE MITOCHONDRIA IN ACUTE EXPERIMENTAL NEPHROSIS DUE TO MERCURIC CHLORIDE*

ROBERT A. MOORE, M.D.

SAMUEL GOLDSTEIN, M.D.

AND

AARON CANOWITZ, M.D.

COLUMBUS, OHIO

Although mitochondria have been known for several decades, little observation has been made of the changes that they undergo in pathologic processes. The literature was recently summarized and critically reviewed by Cowdry.[1]

Believing that a study of the mitochondria of the cells of a single organ in response to various irritating agents would be of value in understanding the mode of action of these agents, we have undertaken to study the response of mitochondria of the kidney to various nephrotoxic agents. This report is the first of these studies. It is concerned with the changes in the renal mitochondria in response to mercuric chloride.

METHOD

White rats derived from the Wistar stock were used exclusively. The mercuric chloride was dissolved in distilled water and injected subcutaneously into the skin of the back.

Two types of experiments were carried out: The first comprehended the administration of a dosage of 40 mg. per kilogram, and postmortem examination of two animals, each day for five days. This dosage was found to kill in about six days. The second comprehended the administration of variable dosages and postmortem examination of all the animals after twenty-four hours. The dosages employed here were 10, 20 and 40 mg. per kilogram. All animals were kept on the regular stock diet of prepared dog biscuit, cracked corn and water ad libitum. In addition, fresh raw liver and cabbage were given once a week.

When an animal was to be killed, it was stunned by a blow on the head. From 2 to 4 cc. of blood was secured by cardiac puncture, and the abdomen was opened and both kidneys were removed. In all cases, the heart was still beating when the kidneys were removed. One kidney was cut in three sagittal sections and placed in Regaud's fixative (20 per cent neutral formaldehyde in 3 per cent bichromate of potassium). The other kidney was cut into thin slices by a sharp razor; the slices were teased apart and studied after being stained with Janus green. Each experiment was run in duplicate. When the two rats used in an experiment were killed,

* Submitted for publication, July 12, 1929.

* From the Department of Pathology, Ohio State University.

* Read at the Twenty-Eighth Annual Meeting of the American Association of Pathology and Bacteriology, Washington, D. C., May 1, 2 and 3, 1928.

1. Cowdry, E. V.: The Reactions of Mitochondria to Cellular Injury, Arch. Path. **1**:237 (Feb.) 1926.

a normal rat (in the same cage and under similar living conditions) was also killed and examined as a control, the tissues of this rat being subjected to the same reagents and processes. This general plan of using two rats for the experiment and one normal rat for the control was preserved throughout.

The urea nitrogen was determined according to the aeration method of Folin, 1 cc. of whole blood (anticoagulant potassium oxalate) being employed.

The blocks of kidney intended for mitochondrial stains were fixed in 20 per cent neutral formaldehyde in 3 per cent potassium bichromate, for three days, the solution being renewed each day; and in 3 per cent bichromate alone for nine days, the solution being changed every three days; washed; dehydrated in alcohol; cleared in chloroform, and embedded in paraffin. Partial serial sections were cut, one to be stained with hematoxylin and eosin, one with Bensley-Cowdry's acid fuchsin-methyl green and one with iron hematoxylin.

The technic has been given in some detail, since the interpretation of mitochondrial changes is extremely difficult even when there is abundant control

General Relations, Structure and Function of Mitochondria as Determined in Experimental Nephrosis Due to Mercuric Chloride

Dosage, Mg.	Lapse of Time Until Animal Was Killed, Hours	Urea N (Average), Mg.	Histologic Changes	Mitochondria of Proximal Convoluted Tubule
10	24	25	None	No change
20	24	37	Cloudy swelling pars recta; proximal convoluted tubules	Perinuclear arrangement; no qualitative change except slight increase in size
40	24	50	Same as above with beginning involvement of remainder of proximal convoluted tubule	Beginning agglutination of perinuclear mitochondria in pars recta; slight fragmentation and agglutination in first and second parts
40	48	120	Same, but slightly more severe	Same, with loss of specific supravital staining
40	72	100	Complete necrosis pars recta; marked cloudy swelling first and second parts; many hyaline casts; fat in pars recta in some cells of few cases	Complete agglutination of mitochondria in third part; moderate agglutination and marked fragmentation in first and second parts; no change in remainder of tubular system

material. All interpretations in the next section of this paper are based on a collective study of: Janus green supravital stains, acid fuchsin-methyl green, iron hematoxylin and hematoxylin and eosin stains of fixed preparations.

OBSERVATIONS

In the animal receiving the smallest dose of mercuric chloride, 1 mg. per hundred grams of body weight for twenty-four hours, there was no detectable change either in ordinary histologic structure or in the mitochondria, but determinations of the blood urea revealed from 23 to 30 mg. per hundred cubic centimeters.

When this dose was increased to 2 mg. per hundred grams of body weight, definite changes resulted both in the mitochondria and in the histologic appearance of the cell. This change was restricted to the third part of the proximal convoluted tubule. Histologically, it consisted of a marked cloudy swelling and granular degeneration of the

epithelial cells. The nuclei of the cells exhibited pyknosis and karyolysis. In some, the whole tubule from basement membrane out was a mass of acidophilic granular débris. This detritus, however, was not homogeneous; on close examination it was seen to be composed of masses of dense, deeply acidophilic material with a loose, coarsely granular débris between. The dense masses were rather sharply defined, and in the center of some was a pale-staining nucleus. After viewing such severely damaged cells, one expected to find the mitochondria completely destroyed. As nearly as could be determined they were in normal amount. They still retained the specific staining reaction with Janus green, but they tended toward a different arrangement. In

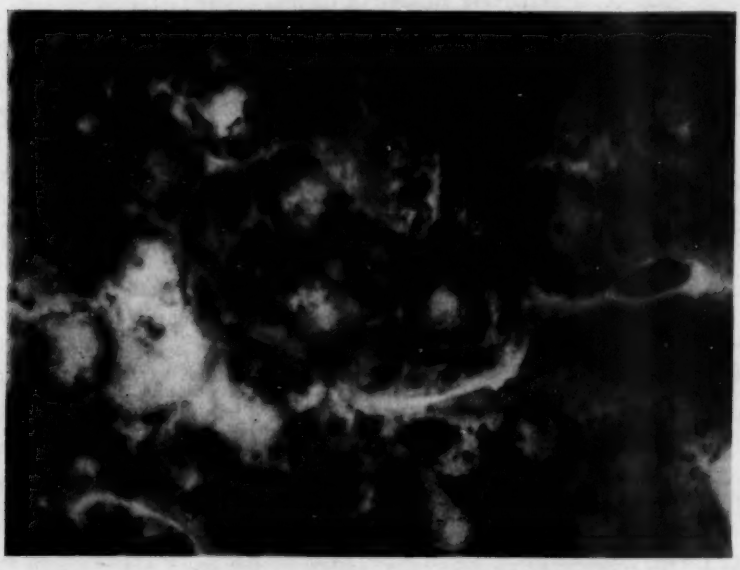


Fig. 1.—An early stage in nephrosis due to mercuric chloride to show the perinuclear arrangement and beginning agglutination of the mitochondria in the third part of the proximal convoluted tubule. Bensley-Cowdry stain.

the normal control, the mitochondria of this portion of the tubule were practically all granular with no definite arrangement, except that they rarely occupied the luminal half of the cell. As a rule, they did not extend beyond the nucleus and if so, only to a slight extent. In the kidney of the animal given mercuric chloride, at this stage the mitochondria were diffuse throughout the cell with a definite perinuclear arrangement in many cases. The masses of protoplasm lying in the lumen look not unlike eosinophilic myelocytes when stained by the acid fuchsin-methyl green method. Although in the majority of cases the mitochondria retained their identity as individual particulate matter, in a few

cases there was a tendency toward agglutination. They appeared to become more highly refractive to light and ran together, finally giving a large, strongly acidophilic, highly refractile mass. In this stage of the disease, these large masses, representing one cell, were not seen to fuse with similar masses, as will be shown later. This change, although definite, was not common at this stage. This early response to mercuric chloride has been discussed at some length, since it is evident that in the injury to the kidney from mercuric chloride, general histologic change and destruction of the mitochondria did not run hand in hand.

With dosages of 4 mg. per hundred grams of body weight, the same tubules showed a marked cloudy swelling and parenchymatous degenera-

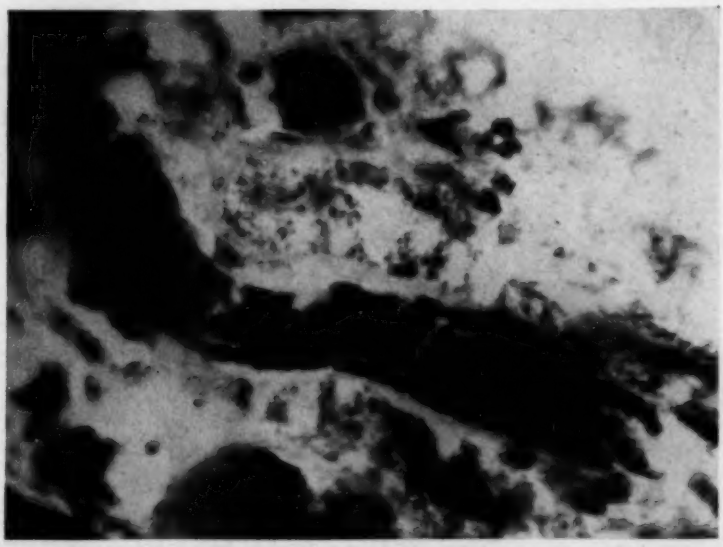


Fig. 2.—A later stage than that shown in figure 1. One may note the large masses of acidophilic material in the lumen. Ordinary stains of such a tubule reveal practically complete necrosis. Bensley-Cowdry stain.

tion of a severe grade. The nuclei were more profoundly affected. In addition to this there was a beginning involvement of the first and second parts of the proximal convoluted tubules. The epithelium was swollen and granular and the nuclei pale staining. The remainder of the tubular system was apparently normal. The mitochondria of the third part of the proximal convoluted tubule were similar to those in the previously described rat, except that agglutination was more marked. Not only were all the mitochondria of one cell fused into a large mass, but four or five mitochondria were seen fusing into a large droplet. On intravital staining, these masses appeared as highly refractile droplets, while the individual mitochondria still stained specifically. The few nuclei remain-

ing in the cells no longer took the methyl green and presented many irregular islands of chromatin, but in each nucleus could be seen one or two large, strongly acidophilic masses resembling nucleoli. Apparently, the basic chromatin had been agglutinated and changed to oxychromatin. In the first and second parts of the proximal convoluted tubule, the chromatin of the nucleus was agglutinated and changed to oxychromatin. The rod-shaped mitochondria were agglutinated into deeply acidophilic masses. Granulation of the rods was not a prominent feature, but in most cases the mitochondria appeared to retain a normal morphology up to the moment of fusion with adjacent rods. The single mitochondria retained their specific supravital staining power, but after fusion lost it.

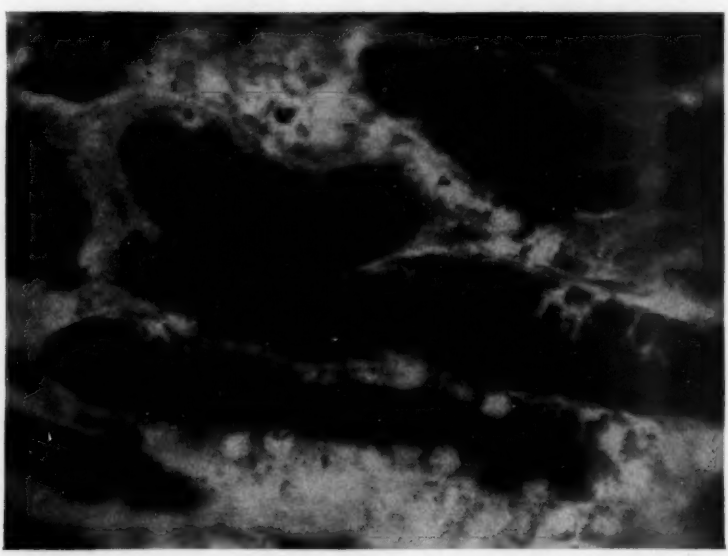


Fig. 3.—A late stage in nephrosis due to mercuric chloride. Three descending limb tubules are filled with necrotic material with complete agglutination of the mitochondria. One may note the one ascending limb with intact mitochondria and its lumen filled with a hyaline cast. Bensley-Cowdry stain.

At this stage, the extremely small rod-shaped mitochondria in the endothelial cells of the glomeruli and in the cells of Bowman's capsule did not differ in morphology from the normal. At this stage, many hyaline casts were to be observed, especially in the distal convoluted tubules. The mitochondria in these tubules even when they contained a cast were regular in shape, size and distribution.

When histologically the tubular epithelium was a homogeneous granular detritus, mitochondria stains gave a deeply acidophilic mass, in some cases somewhat irregular, in others homogeneous. Individual mitochondria could no longer be resolved. The process of agglutination was complete. Even when the process had gone on to complete necrosis

in the third part of the proximal convoluted tubule, the mitochondria and the general appearance of the first part remained fairly well defined. It is only in the most severe nephropathy from mercuric chloride that these cells showed definite agglutination and granulation.

In summary of the mitochondrial changes in the progression of tubular nephrosis due to mercuric chloride in the white rat, it may be said: that the injury even from fairly large doses is definitely restricted to the proximal convoluted tubule, first involving the third portion of the convoluted tubule, later invading the remaining parts; that there are marked histologic changes in the cytoplasm and nucleus with definite retention of nitrogen before the mitochondria show any pathologic

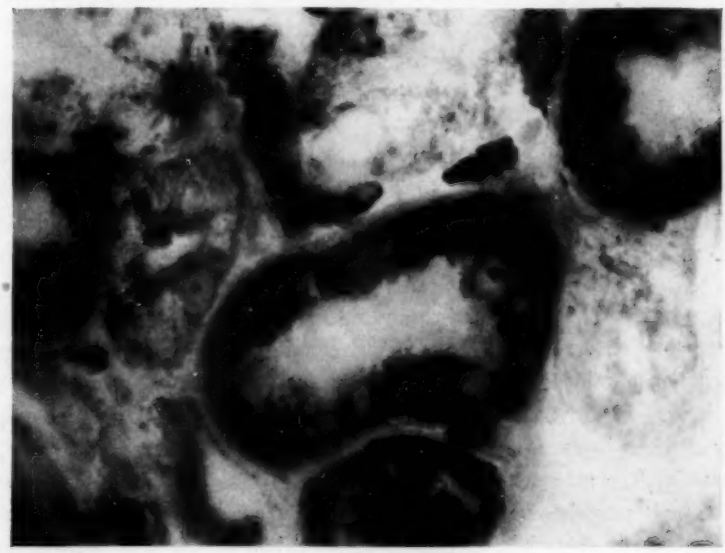


Fig. 4.—A tubule from the upper portion of the proximal convoluted tubule. One may note the prominent acidophilic chromatin mass in one nucleus and the general preservation of rod mitochondria. This kidney showed severe change in the lower portions of the proximal convoluted tubules. Bensley-Cowdry stain.

alteration other than that of position; that morphologically the mitochondrial alteration is essentially an agglutinative process and not a fragmentation of rods into granules; that the chemical nature of the mitochondrial change is not predominantly a fatty metamorphosis, but rather the formation of an acidophilic mass probably albuminous, and finally that there is retention of nitrogen in the blood before there are morphologic changes in the kidney. Function and morphology considered together, the order of events is about as follows: nitrogen retention, parenchymatous degeneration of the cytoplasm, agglutination and to a less extent fragmentation of the mitochondria and, last, complete death of the cell.

COMMENT

From these observations it is evident at once that mitochondria are not always the most sensitive indicator of cell injury. Evidently, the response of mitochondria depends not only on the cell involved, but also on the irritant applied. Strongman [2] and McCann [3] showed that in poliomyelitis, even when the Nissl substance of the nerve cells has undergone partial chromatolysis, the mitochondria retain their usual morphology. Likewise, Marinesco and Tupa [4] demonstrated that the mitochondria of nerve cells are little affected by division of their axones. Against these observations that mitochondria are fairly resistant, we have the fact of their extreme susceptibility in the glandular organs to drying, pressure and other slight mechanical or chemical injury. Further, Oliver [5] observed that in the guinea-pig the mitochondria in the proximal convoluted tubule of the kidney change in morphology during diuresis. He reported granulation of the rods during active urinary secretion, this in some cases going to the point of resembling the definite changes described by others as pathologic. Similar changes have been reported by other investigators. The variability of mitochondrial injury is further emphasized by the observations reported here. Even when the mitochondria of the third part of the proximal tubule are completely destroyed, a distal tubule separated from it only by a few microns presents no deviation from the usual appearance. The final interpretation must be that the injury to mitochondria is dependent on their own inherent properties varying with the cell type and with the nature of the injury. Most emphatically they are not universal indicators of cell injury, as has been assumed by some.

Cowdry,[6] in attempting an explanation of the function of the mitochondria, proposed to utilize the physicochemical phenomenon of adsorption at the mitochondrial cytoplasmic interface. He held that there is an analogy here to the specific adsorption of Janus green. From a 1 : 500,000 solution, mitochondria will concentrate it so that they become visible in a layer 0.5 micron thick. In further support of this, we have the observations of Oliver,[5] using the methods of Leschke. He reported

2. Strongman, B. T.: A Preliminary Experimental Study on the Relation Between Mitochondria and Discharge of Nervous Activity, Anat. Rec. **12**:167, 1917.

3. McCann, G. P.: A Study of Mitochondria in Experimental Poliomyelitis, J. Exper. Med. **27**:31, 1918.

4. Marinesco, G., and Tupa, A.: Recherches histo-pathologiques sur les mitochondries, Compt. rend. Soc. de biol. **87**:292, 1922.

5. Oliver, J.: A Further Study of the Regenerated Epithelium in Chronic Uranium Nephritis, J. Exper. Med. **23**:301, 1916.

6. Cowdry, E. V.: Surface Film Theory of the Function of Mitochondria, Am. Naturalist **60**:157, 1926.

that urea is present in the proximal convoluted tubule in direct proportion to the amount being excreted and that on microchemical precipitation with acid mercuric nitrate, granules are found lined up in the cells in an arrangement similar to that of the mitochondria. The conclusion is that the urea is concentrated or condensed by the mitochondria and that they serve as the means of urea excretion. The position is further strengthened by the observations that the regenerated cells in nephritis due to uranium contain ill defined mitochondria and little or no urea. Interesting also are the observations of different investigators (Aschoff, Gross) that the vital dyes are stored in the proximal tubules by the mitochondria.

The limitations of the applications of morphologic study are not far removed from the simple statement of the observations, yet with the interfacial adsorption theory of Cowdry, it appears that some pathologic conditions may be explained. With ordinary physicochemical adsorption at interfaces, poisoning is a well known phenomenon. For example, platinum black electrodes saturated with hydrogen in a solution of hydrogen ions are rendered useless by a trace of arsenic in the solution. The electrode is said to be "poisoned." In the present report, the observation has been made that there is a retention of urea before the mitochondria are morphologically changed. Assuming that the mitochondria act as condensors to excrete urea, we may postulate that they also condense mercuric chloride and in so doing "poison" the interface so that urea is no longer adsorbed from the blood stream. The result would be a retention of urea in the blood stream. As a mercuric salt is further concentrated by the mitochondria, it comes to a concentration in which it acts on the remainder of the cell and causes its necrosis. The observation that agglutination is a prominent feature in the response of the mitochondria to nephrosis due to mercuric chloride certainly indicates that there is some disturbance in the interfacial tension between the cytoplasm and mitochondria. According to such a theory of the action of mercury in producing renal injury, the initial alteration is an adsorption and "poisoning" of the mitochondrial cytoplasmic interface with a change in the surface tension at this interface. Later, the mercury with increasing concentration acts as a general cytoplasmic poison and kills the entire cell.

SUMMARY

Retention of nitrogen in the blood occurs in nephrosis due to mercuric chloride in the white rat before there are demonstrable changes in the morphology of the kidney. There are definite changes in the cytoplasm and nucleus of the proximal convoluted tubule before the mitochondria show any qualitative change. It is suggested that mercuric chloride produces nephrosis by adsorption on the surface of the mitochondria, "poisoning" the interface and later killing the cell.

PRIMARY CARCINOMA OF LIVER WITH METASTASIS TO BONE*

V. H. MOON, M.D.
PHILADELPHIA

The purpose of this report is to record a primary carcinoma of the liver presenting an extremely rare feature, that of skeletal metastasis. Primary carcinoma of the liver is itself an uncommon lesion, and it rarely forms metastases except in the lungs; in this instance, it gave rise to a large secondary growth in the neck of the femur, causing spontaneous fracture. The neoplastic proliferation was of liver cell type.

REPORT OF CASE

A negro laborer, aged about 45, in the act of lifting, felt his right leg suddenly give way, and he fell to the ground. Previous to this, he had not complained and had worked continuously. Roentgen examination revealed a fracture of the neck of the right femur and evidence of local rarefaction of bony tissue about the fracture. The usual procedure of immobilization in extension and abduction was carried out consistently. There was no evidence of effective healing of the fracture. Six weeks later, the fragments were still mobile, and x-ray pictures showed a deficiency of callus formation. The patient lost weight and strength steadily. Ascites developed, and the fluid was removed repeatedly by cannula. There was no history suggestive of syphilis, but inequality of pupils and a strongly positive Wassermann reaction of the blood caused a suspicion that syphilitic infection of the femur and of the abdominal viscera might be responsible for his condition. Vigorous antisyphilitic treatment was not effective. There developed a progressive anemia of secondary type. The urine contained bile and a small amount of albumin. An indefinite mass was palpable in the epigastric region slightly to the left. An exploratory laparotomy revealed a cirrhotic liver with the possibility of carcinoma or syphilis. The mass consisted of omentum matted together. The abdominal wound did not heal. The patient died nine weeks after the occurrence of the spontaneous fracture. A definite clinical diagnosis had not been made. Bilateral bronchopneumonia, hypostatic in character, was the terminal development.

Postmortem Examination.—The body was that of a markedly emaciated negro about 5 feet 11 inches (150 cm.) tall, apparently 45 years of age and weighing about 90 pounds (40.8 Kg.). The muscles and subcutaneous tissues were wasted. The bony landmarks stood out prominently. The pupils were unequal. Several teeth were missing; the mouth was foul. No lymph nodes other than the inguinal ones were palpable. A surgical wound about 15 cm. in length extended from the level of the tip of the xyphoid process to the level of the umbilicus, slightly to the right of the midline. The deep and the superficial sutures were in place. The wound had gaped for a distance of 4 cm. There was evidence of an imperfect healing process. The right femur was approximately 1¼ inches (3.11 cm.) shorter than the left.

* Submitted for publication, June 25, 1929.

* From the Department of Pathology, Jefferson Medical College.

The right leg was encased in extension bandages of adhesive tape. A palpable mass was present in the region of the great trochanter and neck of the right femur. The mass lay outward from the descending ramus of the ilium and was about 6 cm. in extent, firm and globular. On incision, the mass was found to comprise the neck of the femur and the distended capsule of the joint. The neck of the femur was disunited near the head. The capsule enclosing the joint contained a quantity of curdlike, greenish-yellow material, which was not pus. There was no evidence of callus formation about the ends of the fractured bone. The shaft of the femur below the trochanter was apparently normal, and the outer shell was of normal thickness and consistency. There was no change in the bone-marrow. In the neck of the femur at the point of fracture, the outer shell was not demonstrable, except for a narrow portion in the anterior surface about 8 mm. in width. The ends of this portion were sharp and jagged as if recently fractured. All the rest of the neck of the femur was soft and pulpy. The cancellated bony tissue was eroded extensively, and the remnants of it had greenish-yellow, bile-colored material in the interspaces. The upper rim of the acetabulum was eroded, and on its surface there were quantities of the described bile-colored, curdlike material.

The subcutaneous fat was absent. The skeletal muscles were pale. The omentum did not cover the bowels anteriorly. It was curled up and matted into a mass that occupied the upper portion of the epigastrium. This mass involved the left lobe of the liver and extended to the level of the umbilicus. The right lobe of the liver lay 4 cm. above the costal margin. The pyloric end of the stomach and the duodenum were slightly adherent to the mass described. When separated from it, their structures were found intact. The right lobe of the liver was shrunken, firm and nodular, presenting the typical hob-nailed appearance of atrophic cirrhosis. It cut with increased resistance. On incision, the liver revealed numerous vessels, apparently radicles of the portal vein, containing a yellowish curdlike substance which had a greenish tinge, as if from bile. The tumor mass that involved the left portion of the liver consisted of numerous nodules of a greenish-yellow color and from 0.5 cm. to 2 cm. in diameter. In places, these masses had a putty-like consistence, and varied in color from greenish to brownish. Approximately a hundred such nodules were seen in one section. Numerous such nodules were seen beneath the capsule of the liver.

The portal vein anterior to the foramen of Winslow was completely filled with a mass of soft, pulpy, curdlike, greenish-yellow material similar in all respects to that found in the hepatic branches of the portal vein and in the soft nodules in the liver substance. The mass extended for a distance of 5 cm. along the portal vein. It was found for a short distance below the entrance of the splenic branch. Beyond this point, the portal vein and its mesenteric tributaries were unobstructed.

The wall of the gallbladder was slightly thickened. It showed no involvement by the neoplastic growth. It contained about 60 cc. of black, tarry bile and no concretions.

There were a few adhesions about the upper and posterior portions of each pleural cavity. The right lung was heavy, wet and boggy in its posterior portion, and on section, quantities of blood-tinged, frothy fluid escaped. In the extreme posterior portions, there was almost complete consolidation. The anterior portion contained air throughout and crepitated normally under pressure. The condition of the left lung corresponded with that of the right. Approximately one fourth of the total lung substance was partially consolidated.

The heart was rather small, pale and flabby. The heart valves were apparently normal, and the musculature was of normal firmness.

The intima of the aorta in the ascending portion and the arch contained irregular areas of yellowish and translucent elevations intermixed with puckered and wrinkled depressions. On section, these areas did not contain either calcified or atheromatous material. The descending aorta was not involved.

The spleen was moderately enlarged; its capsule was smooth and contained no scars. On section, an excess of fibrous tissue was found in the splenic pulp. There were no other visible changes.

The entire visceral and parietal peritoneum showed deep injection and was of a purple cyanotic color. The walls of the intestines were relaxed and atonic.

The pancreas was apparently normal. Near the head of the pancreas, were several enlarged lymph nodes. These were grayish white and showed no gross evidence of neoplastic involvement.

There were no other visible abnormalities about the abdominal viscera.

The left kidney was of normal size and configuration. On section, the cortical portion was found increased in thickness and pale. The cortical markings were accentuated, and the capillaries were congested and prominent. A small amount of turbid, apparently purulent fluid could be pressed out of the papillae. The right kidney was somewhat more congested; otherwise it showed the same conditions as the left.

The bladder contained about 100 cc. of brownish, turbid urine. The mucosa appeared to be normal. The musculature of the wall showed no visible changes.

Anatomic Diagnosis.—Primary carcinoma of the liver, with marked destruction and replacement of liver substance; obstruction of the portal vein by the carcinomatous growth; metastatic carcinoma in the neck of the femur, with absorption and destruction of bony tissue, and ununited fracture; atrophic cirrhosis of the liver; bilateral bronchopneumonia; parenchymatous degeneration of the kidneys; toxic degeneration of the heart muscle; fibrosis of the spleen, probably syphilitic; syphilitic aortitis; passive congestion of the abdominal viscera; moderate localized peritonitis; unhealed surgical incision of the abdominal wall; marked generalized emaciation.

Histologic Diagnosis.—Liver: Atrophic cirrhosis; primary carcinoma of the liver cells; carcinomatous masses distending the lumina of the portal veins.

Bone (Neck of Femur): Metastasis of carcinoma from the liver; rarefaction and destruction of the bone substance; deficiency of the healing process.

Lung: Marked passive congestion; metastases of carcinoma from the liver in the peribronchial lymphatics; edema; bronchopneumonia.

Kidney: Congestion; moderate granular degeneration of the tubular epithelium.

Lymph Nodes: Moderate hyperplasia of some; atrophy; fibrosis; beginning calcification of others.

Heart Muscle: Granular degeneration; rarefaction; pigmentation.

Aorta: Degeneration and rarefaction of the intima; cellular infiltration in the adventitia and about vasa vasorum; syphilitic aortitis.

Spleen: Moderate diffuse increase in the stroma; atrophy of the follicles and of the pulp; passive congestion.

Pancreas: Moderate passive congestion; moderate parenchymatous degeneration.

The wall of the bladder, prostate, suprarenal glands and gastro-intestinal mucosa contained no significant features.

Microscopic Examination.—Sections of the liver consisted almost entirely of irregular dense bands of fibrous tissue (fig. 1) enclosing various-sized nodules of carcinoma. Many of these nodules were necrotic; others showed evidence of recent growth and proliferation. All such nodules contained bile pigment, both intracellular and exrtacellular. The carcinomatous cells were slightly smaller than normal liver cells and their cytoplasm was slightly more densely stained. They occurred in dense masses entirely without arrangement. The cells in the masses within the portal veins and in the mass found in the neck of the femur were entirely similar to those in the liver nodules. They also contained bile pigment. The bands of fibrous tissue in the liver were even more dense than those usually found in advanced portal cirrhosis. This fibrous tissue contained numerous proliferated bile ducts and masses of cells representing unsuccessful attempts at bile duct formation. These masses, groups and strands of cells were so irregular

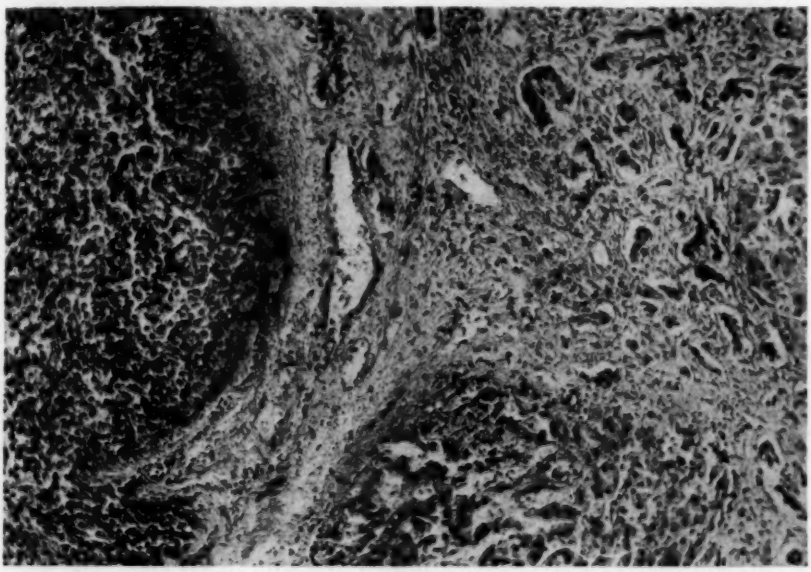


Fig. 1.—Low magnification of a portion of a carcinomatous nodule, showing fibrous tissue containing proliferated bile ducts and groups of fairly normal liver cells.

that they also resembled neoplastic proliferation (fig. 2). Careful study was required to determine this point. There were few areas containing recognizable liver tissue. In such areas, the liver cells were evidently recently formed and seemed to originate directly from bile ducts or from masses of proliferated bile duct cells. There was moderate infiltration by lymphocytes in the bands of fibrous tissue.

Sections from the neck of the femur at the site of the spontaneous fracture showed marked rarefaction and absorption of the trabeculae of the cancellated portion and of the outer shell of compact bone. The spaces in the spongy portion contained no marrow cells or fat, but were filled with masses of neoplastic cells having the same characteristics as those seen in the liver and in the thrombotic masses in the portal veins (fig. 3 *B* and *C*). These cells contained bile pigment,

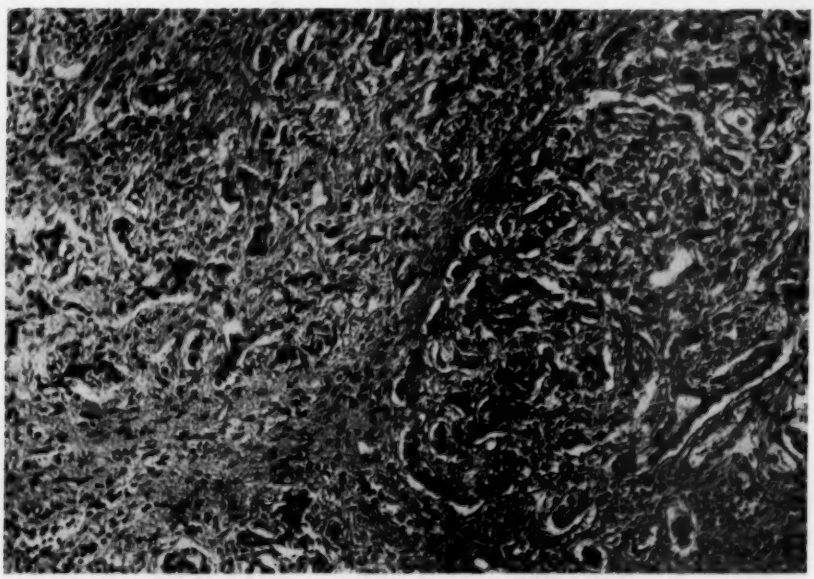
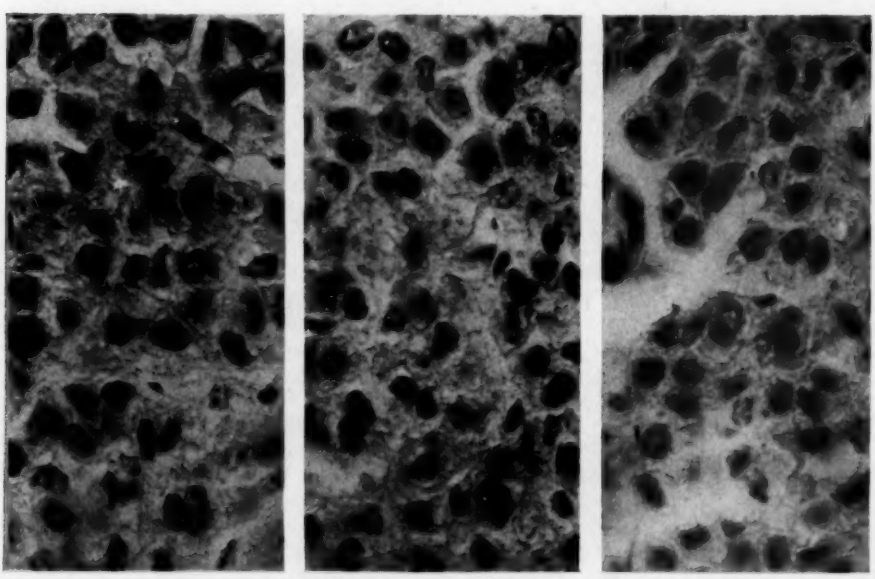


Fig. 2.—Low magnification of fibrous tissue with leukocytic infiltration. This area contains a proliferation of bile ducts so irregular that it resembles neoplastic growth of bile ducts.



A B C

Fig. 3.—The 4 mm. objective, ocular × 10, was used here. One may note carcinomatous cells in a liver nodule (*A*); growth at the site of spontaneous fracture (*B*); the thrombotic mass in the portal vein (*C*).

as did the neoplastic cells in the other locations. This observation suggests that bile pigment is formed by the cells of the liver rather than elsewhere in the body, and that the carcinomatous cells in this case retained that functional capacity. There were small areas of soft, imperfect newly formed bone, which was immature and showed no calcification.

Sections from the lung showed small masses of carcinomatous cells within the lymph spaces along the bronchial structures. No masses visible to the unaided eye were found. The cells in the lymph spaces had the characteristics of those seen in the nodules in the liver, in the thrombi within the portal veins and in the metastasis in the femur.

Cases of primary carcinoma of the liver with metastasis to bone are rare. Kauffmann [1] recorded two such cases. In one there were metastases in the vertebral bodies, ribs, lungs and lymph nodes; in the other, there were metastases in the abdominal lymph nodes and sternum. Catsaras [2] reported one case of liver cell carcinoma, with metastases in the head and neck of the right femur resulting in spontaneous fracture of the shaft below the great trochanter. Schmidt [3] reported a case with metastases in the frontal bone, the sternum and the pelvis. In this case, metastases were also present in the dura and the lungs. Extension of the growth had involved the portal vein. Blumberg [4] reported a case in which there was metastatic involvement of the twelfth dorsal vertebra and of the kidney. I have been unable to find record of other cases of skeletal metastases arising from primary carcinoma of the liver.

---

1. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7, Berlin, Walter de Gruyter & Co., 1922, vol. 1, p. 755.
2. Catsaras, J.: Ann. de méd. **10**:295, 1921.
3. Schmidt, M. B.: Virchows Arch f. path. Anat. **148**:43, 1897.
4. Blumberg: Frankfurt. Ztschr. f. Path. **10**:186, 1912.

WHOOPING COUGH

THE SITE OF THE LESION *

LOUIS W. SAUER, M.D.
AND
LEONORA HAMBRECHT, A.B.
EVANSTON, ILL.

The study of the specific lesions in pertussis is usually based on human material with fatal pulmonary involvement. Arnheim's [1] pioneer work on the microscopic examination of expectorated mucus and stained sections of the respiratory tract appeared before Bordet and Gengou [2] had announced the discovery of *Bacillus pertussis*. Mallory and Hornor [3] found in fatal whooping cough an abundance of pertussis-like bacilli between the cilia of the trachea and bronchi. They described no characteristic lesion, and inferred that the trachea was mainly involved. Heinrichsbauer [4] recently substantiated Dominici's [5] observation that in fatal pertussis the larynx may show microscopic areas of necrosis. This lesion is not specific, as it was not constant, and was found also in fatal measles. Pospischill [6] has long maintained that "pertussis seems to be anchored in the lung; here is found its essential, most important and clinically classic manifestation." Feyrter's [7] excellent monograph on the lesions of the lung in pertussis was based on 225 postmortem examinations, in 100 of which he studied the material histologically. The investigation did not include the rest of the respiratory tract, nor any detailed study of the bacteria. He said, in summary: "The lung becomes diseased early in the course of pertussis. . . . Pertussis peribronchitis is the cause of the frequent long duration of pertussis lung disease. . . . In the bronchiolitis and peribronchio-

* Submitted for publication, Sept. 18, 1929.

* From the Evanston Hospital.

1. Arnheim, G.: Zur Pathogenese des Keuchhustens, Berl. klin. Wchnschr. **29**:665, 1903.

2. Bordet, J., and Gengou, O.: Le microbe de la coqueluche, Ann. de l'inst. Pasteur **20**:731, 1906.

3. Mallory, F., and Hornor, A.: Pertussis: The Histological Lesion, J. M. Research **27**:115, 1912.

4. Heinrichsbauer, F.: Ueber mikroscopische Veränderungen im Kehlkopf beim Keuchhusten, Jahrb. f. Kinderh. **118**:104, 1927

5. Dominici, L.: Contributo allo studio anatomo-pathologico della pertosse, Riv. di clin. pediat. **5**:901, 1907.

6. Pospischill, D.: Ueber die Klinik der Pertussis, Berlin, S. Karger, 1921, p. 31.

7. Feyrter, F.: Pathologische Anatomie der Lungenveränderungen beim Keuchhusten, Frankfurt. Ztschr. f. Path. **35**:213, 1927.

litis (not in the bronchitis) does pertussis bronchopneumonia have its origin." Smith [8] found *B. pertussis* not only in the trachea and bronchi, but also in the alveoli in seven of eight fatal cases of pertussis bronchopneumonia.

MATERIAL

Our work on experimental pertussis in young monkeys [9] provided exceptional material for study of the respiratory tract in benign pertussis and in early pertussis bronchopneumonia. The complete respiratory tract of one infant (Peter K.) and the larynx, trachea and bronchi of three others who died of convulsions in the catarrhal stage or early in the paroyxsmal stage were also available.[10] This investigation deals primarily with the regional bacteria and the histologic changes of the larynx, trachea, bronchial tree and alveolar parenchyma. Ringtail monkey R2 was chosen because the course of the disease in this animal resembled that commonly encountered in young children who recover without complications. Infant Peter K. died at the onset of pertussis bronchopneumonia twelve days after the cough began. Rhesus monkey A5 had severe paroxysms for a week before he showed clinical signs of pertussis bronchopneumonia. The postmortem examinations were performed while body heat was still present. After the respiratory tract of each was examined with a hand lens for visible changes, smears and cultures were taken of larynx, trachea, bronchi and lungs. Pieces of the fixed specimens were embedded in paraffin and sectioned. Of the various stains used that of Gram, counterstained with carbolfuchsin, proved best for bacteria and cilia, whereas hematoxylin-eosin gave the best differentiation for the histologic material.

OBSERVATIONS

Two young male ringtail monkeys (R1 and R2) arrived on Dec. 31, 1925. The respective weights were 1,700 Gm. and 2,000 Gm.; the hemoglobin was 70 and 75 per cent; the average leukocyte counts were 7,350 and 9,100 per cubic millimeter. They resisted several nasal and throat inoculations with *B. pertussis*. On Jan. 25, 1926, they were given 2 cc. of a fresh *B. pertussis* suspension intralaryngeally. February 2 both animals sneezed and had a slight, infrequent cough. During the following days, the cough increased in severity and frequency. Within a week, they coughed in paroxysms. Lacrimation frequently accompanied the paroxysms of coughing. Many consisted of more than 20 "hacks." Never was a characteristic whoop heard. The leukocyte count in R2 exceeded 38,000, and lymphocytosis reached 89 per cent. They vomited mucus at the end of severe paroxysms, after which they usually appeared exhausted. February 13, the cough was not growing worse, and lymphocytosis had decreased. As both animals were apparently recovering, R2 was killed for study of the respiratory tract.

Monkey R2.—The essential postmortem observations were as follows: The lining of the epiglottis, larynx and trachea was pale and pearly white, except for three minute, bright red hemorrhagic areas in the wall of the larynx. The largest measured 4 by 2 mm., the smallest, 2 by 2 mm., the other, 3 by 2 mm. There was some tenacious, transparent mucus in this vicinity. Smears contained leukocytes

8. Smith, L.: The Pathologic Anatomy of Pertussis, Arch. Path. **4**:732 (Nov.) 1927.

9. Sauer, L., and Hambrecht, L.: Experimental Whooping Cough, Am. J. Dis. Child. **37**:732 (April) 1929.

10. These specimens were kindly sent by Professor Feyrter.

and an abundance of gram-negative bacilli. No other micro-organisms were found. There were several barely visible, superficial hemorrhagic spots on the posterior tracheal wall just below the larynx; otherwise the surface of the trachea was pale, smooth and glistening. The lungs appeared normal in color and consistency; the surface was smooth, and when the material was sectioned, no areas of consolidation or other changes were seen. The tracheobronchial lymph glands were slightly enlarged.

Examination of stained sections of the larynx failed to reveal the minute hemorrhagic areas described, nor was anything resembling a lesion found. Most of the cilia were intact, and relatively few bacilli were found between and on them. Stained sections of the trachea showed in places aggregations of pertussis-like bacilli. The epithelium and submucosa appeared normal without any signs of inflammation.

Examined under low power, stained sections of the lung appeared more or less normal. The larger bronchi were relatively free from content; some had a thin layer of mucus and débris in contact with the epithelial layer. A few of the smaller bronchi contained mucus, débris and cell elements, and had definite infiltration of the epithelium and submucosa. One was found in which the lumen was almost filled. There were regions of atelectasis in the vicinity of these smaller bronchi. Here the alveolar septums appeared definitely thickened and infiltrated, and some of these alveoli were filled with cell elements. The blood vessels were not engorged, but a few of the larger ones lying near diseased bronchi had adjacent areas of infiltration (fig. 1*A*).

Under oil immersion, the mucus and débris in the large bronchi contained polymorphonuclear leukocytes and occasional mononuclear cells. In the submucosa there were aggregations of polymorphonuclear leukocytes. The material which partly filled some of the smaller bronchi consisted of desquamated epithelium, lymphocytes, plasma cells, mast cells and a few polymorphonuclear leukocytes. The epithelium and submucosa of these bronchi showed definite infiltration with round cells. On the ciliated epithelium of some of the bronchi, clusters of pertussis-like bacilli were seen. The areas of infiltration adjacent to some of the larger blood vessels consisted of lymphocytes, plasma cells and mast cells. These changes showed the presence of endobronchitis with a slight degree of peribronchitis. Some of the bronchioles showed similar infiltration but of less degree. On the epithelium, a few pertussis-like bacilli were seen (fig. 1*B*). Capillaries in the vicinity of a bronchiole which had its lumen partly filled appeared somewhat infiltrated. There was a mild endobronchiolitis and peribronchiolitis. All the alveoli, except those in the vicinity of diseased bronchi, appeared normal. Bacilli were never found in them, although diligently searched for.

Peter K.—The infant, Peter K., aged 3½ months, had never been ill until he contracted pertussis from his sister, in spite of three "prophylactic" injections of pertussis vaccine as soon as the diagnosis had been made in the older child.[11] The cough began twelve days before death. The paroxysms became severe twenty-four hours before admission to the hospital. He never whooped. When admitted (five hours before death) he was having convulsions, with cyanosis during paroxysms, and rapid, audible respirations. The rectal temperature was 106 F. (41 C.); the pulse, 160; the respirations, 60. Shortly before death, the child expectorated tenacious, dark red, frothy mucopus. Clinical diagnosis: Pertussis with convulsions and beginning bronchopenumonia.

11. Sauer, L., and Hambrecht, L.: Whooping Cough, Vaccine Therapy or Early Diagnosis, J. A. M. A. **91**:1861 (Dec. 15) 1928.

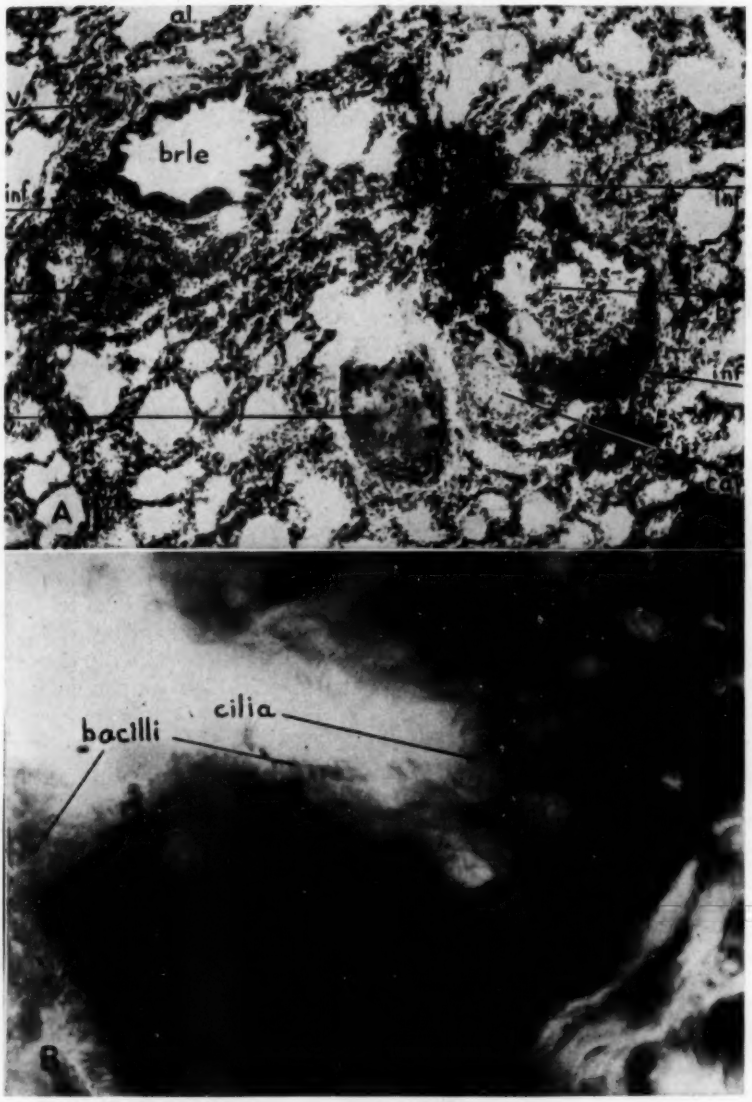


Fig. 1 (ringtail R2).—Experimental pertussis. *A,* lung showing endobronchitis and peribronchitis; × 70. *Al* indicates alveolus; *br,* bronchus; *brle,* bronchiole; *car,* cartilage; *inf,* infiltration, and *v,* vessel. *B,* bronchiole, showing ciliated epithelium with pertussis-like bacilli; × 1,500.

Dr. J. Lisle Williams' postmortem report (abridged) was as follows: "This is the body of a well developed male infant, about 3 months old, weighing about 12 pounds (5.4 Kg.). . . . The lining of the nasopharynx, epiglottis, larynx and trachea is smooth and pale. There is a little thin mucus in the trachea. . . . The tracheobronchial lymph glands are slightly enlarged, soft and pink. The lining of the left main bronchus contains only mucus in both the lower and eparterial branches. . . . The pleural sacs are normally free, and are free of fluid. In the back part of the upper and lower lobes of the right lung there are about 15 small, dark red and partially consolidated patches; in the back part of the left lower lobe there are a few, small, similar places. . . . Surfaces made by sectioning the right and left lungs disclose these dark red areas (sections). Some of these patches which are adjacent to the pleural surface resemble atelectasis.

"Microscopic: . . . Lungs: Here are seen small areas in which the alveoli are filled with fibrin, leukocytes and erythrocytes; numerous small patches of atelectasis, chiefly about the bronchi; increased fibrous tissue about the bronchi with lymphocytic and leukocytic infiltration. The bronchi are filled with leukocytes, lymphocytes, desquamated epithelium and granular débris. There is engorgement of the capillaries, especially about the bronchi and in the areas of bronchopneumonia. . . ."

Examination of stained sections of the larynx revealed nothing resembling a lesion. Most of the cilia were intact, and relatively few bacilli were found on or between them. Sections of the trachea showed aggregations of gram-negative bacilli; the epithelium and submucosa appeared normal with no sign of inflammation.

Under the hand lens, the stained sections of the diseased areas of the lung showed regional atelectasis and dense infiltration, most pronounced around bronchi and blood vessels. This density was in direct proportion to their proximity. The blood vessels in these centers appeared congested; the alveolar tissue beyond was more or less air-containing, with occasional areas of emphysema.

Under low power, the lumina of some bronchi were filled; others were relatively free. The epithelial walls of the filled bronchi showed extensive infiltration; the submucosa was likewise infiltrated. Here one is dealing with severe endobronchitis and peribronchitis (fig. 2*A*). Some of the bronchioles showed such a degree of infiltration that they were completely obliterated, endobronchiolitis obliterans (fig. 2*B*). Endobronchiolitis and peribronchiolitis were pronounced. The capillaries here, as well as those immediately beyond the diseased bronchi, were greatly congested. The areas of most intense infiltration were found between diseased bronchi and large blood vessels. The region adjacent to the opposite wall of such vessels was free from this intense inflammation. The capillary blood appeared normal. Most of the alveoli near the diseased bronchi contained débris or extravasated blood. The alveolar walls which showed the greatest degree of infiltration were those adjacent to diseased bronchi. Midway between such centers of inflammation, the lung tissue appeared more normal, but some of the alveolar walls were exceedingly thin, the alveoli were greatly distended with air, and some had ruptured because of the emphysema.

Under oil immersion, the diseased bronchi revealed a content of desquamated epithelial cells, round cells, polymorphonuclear leukocytes and bacilli which resembled *B. pertussis*. The walls of such bronchi were intensely infiltrated with polymorphonuclear leukocytes and cells of the round type. These cells also appeared in abundance in the submucosa which, like the epithelial wall, in places, was partly obliterated by invading cells. The aforementioned zone of infiltration

which lay between the large blood vessels and the bronchi consisted mainly of cells of the round type. Where the epithelium had desquamated, cells from the submucosa had reached the lumen. Some of the more or less intact cilia were thickly embedded with pertussis-like bacilli. Such bacilli were seen in abundance where

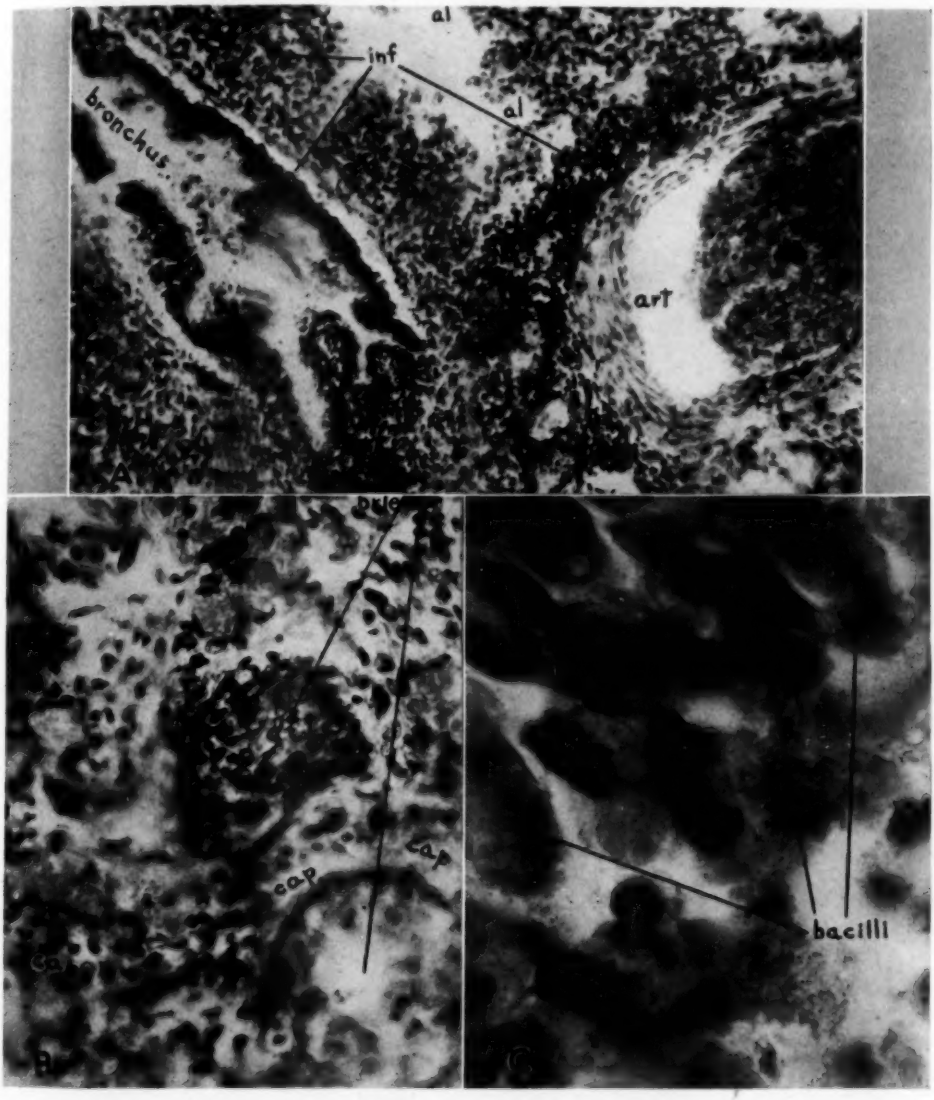


Fig. 2 (Peter K.).—*A*, lung, showing pronounced endobronchitis and peribronchitis, adjacent alveoli (*al*) completely atelectatic and a heavy zone of infiltration (*inf*) about blood vessel (*art*). adjacent to diseased bronchus; (× 160); *B*, two bronchioles (*brle*) separated by capillary (*cap*). The one above is completely obliterated; the one below contains pertussis-like bacilli and cells; × 350. *C*, ciliated epithelium of a large bronchus, heavily laden with pertussis-like bacilli. The epithelial structure is obliterated by cell infiltration; × 1,500.

tissue changes were most profound (fig. 2*C*). The endothelium of the capillary walls in the submucosa had proliferated. These capillaries were filled with leukocytes, some of which were passing through the wall toward the diseased bronchioles. The bronchioles showed changes similar to those described for the bronchi. The lumina of completely obliterated bronchioles were filled with plasma cells, mast cells, lymphocytes, polymorphonuclear leukocytes, erythrocytes, pertussis-like bacilli and fibrin (fig. 2*B*). In some of the patent bronchioles polymorphonuclear leukocytes were abundant. The marked peribronchitis was due to round-cell infiltration. The alveolar walls in these parts were definitely thickened and infiltrated; the alveoli were more or less atelectatic. Some were compressed, others were filled with fresh blood or round cells and polymorphonuclear leukocytes. Pertussis-like bacilli were seen in a number of them.

Rhesus A5.—This young male monkey arrived on Sept. 10, 1927. He weighed 1,600 Gm. The hemoglobin tested 80 per cent. The average leukocyte count for the eighteen days before inoculation was 16,837; the differential blood count was: polymorphonuclears, 48; small lymphocytes, 29; large lymphocytes, 15; eosinophils, 8. Oct. 1, 1927, 1.5 cc. of a two-day growth of *B. pertussis,* strain "Webber," was dropped into the nares. After a week, the animal presented rhinitis, sneezed and coughed. The leukocyte count had reached 59,750; the differential blood count was: polymorphonuclears, 32; small lymphocytes, 57; large lymphocytes, 11. October 10, the nasal and throat cultures were positive for *B. pertussis;* no distemper bacilli were found. The following day, the cough increased in frequency and severity. By October 12, the cough was severe; during one hour, the animal had nine attacks of coughing. October 14, the leukocyte count was 89,400. The animal appeared very ill, and as the percentage of polymorphonuclear leukocytes was increasing, pulmonary involvement was suspected, and the animal was killed for study of the respiratory tract.

The essential postmortem observations were as follows: The lining of the epiglottis, larynx and trachea was pale and pearly white throughout. The lower part of the trachea contained an excess of yellow mucus. *B. pertussis* was found in smears and cultures from the larynx and trachea, but more colonies were obtained from laryngeal mucus. The tracheobronchial lymph glands were somewhat enlarged. Several small, dark red areas were scattered over the posterior part of both lungs, especially in the lower lobe of the right lung. When these areas were cut through, they were found to be consolidated. *B. pertussis* was recovered in smears and cultures from these areas. No other micro-organisms were found. (The recovered bacillus was subsequently inoculated into *Rhesus* A4, which presented a paroxysmal cough seven days later.)

Sections of the larynx showed the ciliated epithelium intact; no lesion was found. Mucus and abundant pertussis-like bacilli were present. In sections of the trachea, many similar bacilli were found on and between the cilia, which appeared intact. The mucus glands did not show involvement, nor did they contain bacilli, despite the fact that many pertussis-like bacilli lined the trachea. No infiltration of the tissues was seen, except in one area which showed superficial necrosis. Here desquamation of the epithelium had occurred, with some infiltration of the submucosa. Pertussis-like bacilli were present in masses on the desquamated epithelium.

Examined with a hand lens, stained sections of the consolidated areas of the lung showed marked infiltration in the immediate vicinity of the bronchi. The largest bronchi contained relatively less débris than did the smaller ones. The density and extent of the infiltration around the bronchi appeared to be in direct proportion to their size.

Under low power, there was marked engorgement of all blood vessels, especially in the region of diseased bronchi. The lumina of some bronchi contained débris, which completely filled some of the smaller ones. The submucosa was thickened and infiltrated, as was also the tissue beyond the elastic layer. There were endobronchitis and marked peribronchitis. About some of the larger bronchi a deeply staining zone of infiltration, greatly thickened in places, surrounded bronchus, cartilage and blood vessels, so that the alveoli appeared completely separated from them. The alveolar tissue in the immediate vicinity of such bronchi showed extensive infiltration, and many of the alveoli appeared completely filled. Farther distant alveoli contained more or less air; some were emphysematous, and the septal walls appeared thickened. Some of the bronchioles showed an intense infiltration with a wide zone of involvement about them. Some of their lumina were filled. Figure 3 shows such a bronchiole (endobronchiolitis and peribronchiolitis).

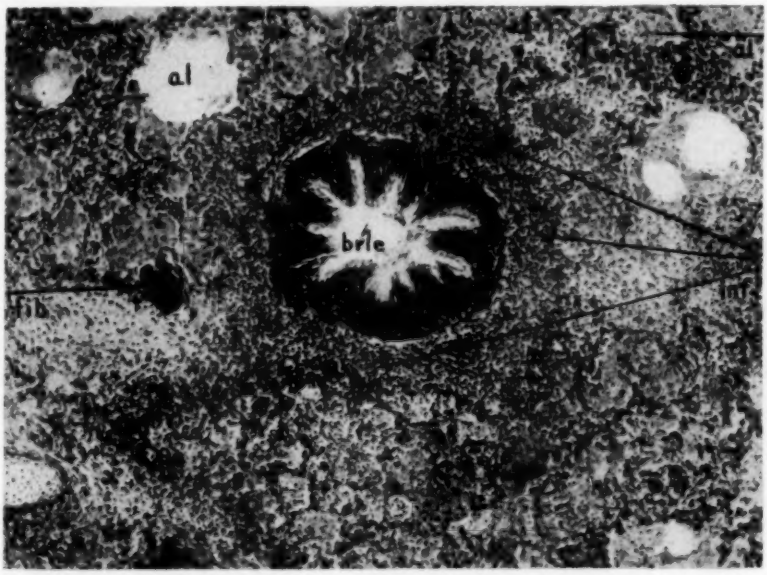


Fig. 3 (Rhesus A5).—Experimental pertussis. A bronchiole (*brle*) is shown with heavily stained epithelium and infiltrated submucosa (endobronchiolitis and peribronchiolitis); × 70.

Under oil immersion, the granular débris in the bronchi consisted of desquamated epithelium, mucus, erythrocytes, polymorphonuclear leukocytes, round cells and pertussis-like bacilli. The columnar cells of the epithelial layer appeared edematous, with the nuclei staining deeply. This layer, on the whole, appeared well intact. In certain areas in which desquamation had occurred, the desquamated cells had become round or cuboidal. There was little cell infiltration of the wall; an occasional polymorphonuclear leukocyte, lymphocyte, plasma cell or mast cell could be seen between the cells. In many areas, the cilia appeared normal; in others, they were missing. Pertussis-like organisms were found on and between some of the cilia.

In that part of the submucosa adjacent to the elastic layer, polymorphonuclear leukocytes were abundant, and in certain areas occurred in dense aggregations. Round

cells predominated in the densely infiltrated areas beyond. The epithelial cells of the bronchioles likewise appeared edematous, and the nuclei of the cells stained deeply. There was little cell infiltration of this layer. Some of the cilia of the bronchioles were densely studded with pertussis-like organisms. The infiltration of the submucosa of the bronchioles was due mainly to cells of the round type, with some polymorphonuclear leukocytes present. Most of the alveoli in the areas of infiltration contained leukocytes, round cells, fibrin, pertussis-like bacilli and erythrocytes. The alveolar parenchyma was likewise infiltrated. The congestion of the capillaries and the free blood in the alveoli near the diseased bronchi formed a striking contrast to the more normal tissue at the periphery. No gram-positive organisms were found. Cultures of these parts post mortem revealed only the Bordet bacillus. The numerous, transversely cut capillaries in the alveolar tissue showed markedly infiltrated walls; their lumina were filled with polymorphonuclear leukocytes, erythrocytes and desquamated endothelial cells.

COMMENT

If a susceptible child aspirates pertussis bacilli expelled by a coughing patient, the disease may develop after an incubation period of at least a week. A cough-plate, properly exposed during the catarrhal or early paroxysmal stage, should show colonies of *B. pertussis* within four days. The "pearls" of bronchial mucus coughed up during this time contain *B. pertussis,* often in nearly a pure state, also leukocytes, lymphocytes and desquamated epithelium. This evidence of injury by the toxin of the causative organism shows that early in the disease the bronchi are involved. The presence of bacilli on and between intact cilia in stained sections of the larynx and trachea without visible tissue changes leads one to suspect that the lesion is farther down the bronchial tree. The not infrequent presence of unique râles (Pospischill [6]) during the catarrhal stage is clinical proof that the seat of the infection is in the lung.

Search for the region that showed the most profound injury in uncomplicated experimental pertussis led to the finer bronchi and bronchioles. The microscopic study of the respiratory tract of monkey R2 (without macroscopic pulmonary involvement) offered strong evidence that the bacilli reached the finer branchings of the bronchial tree. Endobronchitis and peribronchitis were more pronounced than were endobronchiolitis and peribronchiolitis. No pertussis-like organisms were found in the alveoli. In Peter K. and Rhesus A5 who showed macroscopic pulmonary changes there was marked involvement of the bronchi, bronchioles and adjacent alveoli. Pertussis-like bacilli were found in abundance in these areas. Endobronchiolitis and peribronchiolitis were as pronounced as were endobronchitis and peribronchitis. Since the bronchioles showed more involvement than those in R2, and as alveolar involvement occurred only in regions adjacent to diseased bronchi and bronchioles, one infers that the bacilli reach the alveoli by way of the respiratory tract, rather than by way of the blood stream. The peri-

vascular infiltration appears to be a protective reaction (fig. 2A). Cells of the round type—lymphocytes, plasma cells and mast cells—predominate in the areas of most profound injury. The response to the invasion of the lung by *B. pertussis* is more proliferative than inflammatory.

SUMMARY

The bronchi (and bronchioles) are the primary seat of infection in uncomplicated, experimental pertussis. Endobronchitis and peribronchitis are more pronounced than are endobronchiolitis and peribronchiolitis. The latter are more pronounced in human pertussis with early bronchopneumonia and in experimental pertussis with early bronchopneumonia. Alveolar involvement occurs by way of the bronchioles. Only pertussis-like bacilli are found on and between the cilia of the finer bronchi and bronchioles in uncomplicated experimental pertussis; in human pertussis bronchopneumonia and in experimental pertussis bronchopneumonia, they are found also in the alveoli. Mucopurulent inflammation is soon replaced by round cell infiltration, which is most pronounced where the injury is most profound.

General Review

THE THYROID GLAND IN HYPERTHYROIDISM*

FRANK R. MENNE, M.D.
PORTLAND, ORE.

The wide variation in the secretory activities of the thyroid gland in different persons is reflected in the many disease processes now recognized as having their origin in disturbances of the gland's anatomic structure. The contributions (variously estimated from 8,000 to 10,000) devoted to the experimental, clinical and pathologic aspects of the problem of goiter have brought its solution nearer. In general, there is now recognized the specific rôle of the thyroid gland as a regulator of metabolism (catabolism, in particular) in proportion to the output of its hormone and the responsiveness of the tissues to the hormone. There are recognized two definite clinical manifestations, hyposecretion and hypersecretion. There is also evidence of the possible production of a perverted secretion. The former two possible functions have given rise to the many interesting clinical phenomena which have been associated with the variable pathologic changes in the thyroid gland.

Knowledge of the thyroid gland in hypersecretion of its hormone has grown insidiously from the imaginative records of the early physicians, who had no knowledge of its structure or function, to the present more accurate observations.

Early considerations of the clinical manifestations of hyperthyroidism had to do with the effect of thyroid enlargements on respiration. The only comments on the changes in the gland were those casually made in connection with the more accentuated early forms of therapy. Although Paracelsus (sixteenth century) definitely established the relationship between endemic goiter and cretinism, definite knowledge of the thyroid dates from the descriptions of it by Vesalius (1543) and Thomas Wharton (1656) and its later classification as a ductless gland by Haller (1776).

While there are many clinical accounts of the nature and evidences of swellings of the neck in association with cretinism or early unnamed myxedema, there is a striking absence of observations of the clinical manifestations which are now known to indicate hyperthyroidism. That such conditions existed is unquestionable, but the failure to observe some

* Submitted for publication, Feb. 20, 1929.

* From the Department of Pathology, The University of Oregon Medical School.

of the symptoms is not so easily understood. In testimony of their existence in former times, Van Leersum [1] pointed to the characteristic types in some of the paintings of the old Flemish, Dutch and German masters, who often reproduced their models too accurately to hide their physical defects. Bilateral or unilateral symmetrical swellings of the thyroid gland with staring eyes and widened palpebral fissures and lean figures were often vividly portrayed.

To Parry [2] belongs the credit of the association of palpitation of the heart with enlargement of the thyroid. An excerpt from his writing reads as follows: "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland. The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1786." Parry's full report indicates that he studied three instances of primary hyperthyroidism and two of so-called secondary hyperthyroidism (in women, aged 40 and 50). He described the glands as large, extending half way up the sternocleidomastoid muscles and lying anterior to the pulsating carotid arteries. One of the gland disorders started as a nodule on the right side, but soon spread over the rest of the gland. The records of these few instances and the meager descriptions of the thyroid glands in them constitute the basis of the present enormous superstructure of clinical, pathologic, experimental and etiologic studies concerning its disturbances.

During the seventy years that followed, innumerable clinical observations were made, among which are those of Graves (1835) and Basedow (1840), who pointed out certain definite characteristic symptoms, so that later the condition was designated, by their names, Graves' or Basedow's disease. During this time, the pathologic anatomy of the thyroid received little attention. Surgical removal, although practiced on animals (Schiff, 1859), when attempted on human beings, ended with disastrous results. Watson [3] is given credit for having done the first surgical removal in a case of exophthalmic goiter, a feat that required daring, since surgical treatment of any form of goiter at that time was condemned because of the serious consequences. Schill (1879) reviewed thirty-four articles in the French, German and English literature. He quoted Briere as stating that extirpation of goiter was carried out twenty-nine times during the period from 1785 to 1845; eleven of the

1. Van Leersum: Arch. internat. pour l'histoire de la méd. a la geog. méd. **29**:282, 1925.

2. Parry, C. H.: Collections from the Unpublished Medical Writings, London, Underwood, 1825, vol. 2, p. 3.

3. Watson: Edinburgh M. J. **19**:252, 1875.

patients died. Between 1845 and 1871, forty-four cases of operation were reported on; twelve of the patients died. Kicher reported a mortality of 19 per cent. In other clinics, the mortality was as high as 40 per cent (Susskind). The total number of such excisions to 1876 was 162. In most of the reports of instances in which operation was done, only brief mention is made of the pathologic nature of the gland, and the notations were largely the result of preoperative clinical observations. Graves,[4] discussing the disturbances in the thyroid gland in three instances, said that "they (the thyroid glands) are considerably larger than natural." He spoke of a "sudden interstitial effusion of blood into the thyroid," which he regarded as "slightly analogous in structure to the tissues called erectile." He preferred to view the changes as hypertrophies. Among the subsequent descriptive terms occurring in the literature, two probably referred to the hypersecreting thyroid gland, namely, parenchymatous goiter and vascular goiter. This dearth of distinctive study of the anatomic changes in the thyroid was probably due to the confusion resulting from the many opinions as to the etiology summed up by Klose and Helwig[5] as follows:

1. The constitutional theory (von Buschan): There was thought to be a secondary involvement of the thyroid gland.

2. The bulbar theory: The seat of the trouble was thought to be in the medulla oblongata and midbrain.

3. The central theory: Cortical lesions were held responsible.

4. The theory of hyperthyroidism and dysthyroidism: The occurrence of an increased or decreased thyroid secretion was suggested.

5. The theory of hypothyroidism: The thyroid was not thought to be a gland of internal secretion but a filter for the blood poisons; its failure of function led to auto-intoxication.

6. The theory of polyglandular disease: The entire endocrine system was considered to be damaged.

7. The sympathetic theory: The disturbance was considered to affect the sympathetic nervous system.

Such theories had their adherents who industriously defended them and accordingly directed their attention to the pathologic anatomy of the organs and tissues concerned. The pathologic anatomy of thyroid enlargements, in general, and those changes underlying exophthalmic goiter, in particular, were touched on only in scattered statements included in clinical dissertations in which the etiology, symptomatology and therapy received the most attention. Pathologic classifications were largely individual concepts, often specifically including the therapy recommended. One of these by Leveque (1872), recorded by Schill,[6] is

4. Graves: Clinical Lectures, Dublin, Fannin & Company, 1848, p. 150.
5. Klose and Helwig: Klin. Wchnschr. **2**:627, 1923.
6. Schill: Schmidt's Jahrb. **182**:177, 1879.

of interest because of the evidence contained therein of the early use of iodine. Leveque's classification was as follows: "1. Parenchymatous goiter—Iodine internally and externally, iodine injections. 2. Fibrose goiter—Iodine injections, hair setons. 3. Colloid goiter—Iodine internally and externally, hair setons. 4. Cystic goiter—Puncture, drainage, hair setons. 5. Vascular goiter—Chloride of iron injections."

A greater impetus was given the study of the changes in the thyroid (1) by such experiences as that of Kocher (1883),[7] in which he removed the entire organ in exophthalmic goiter and found it to be vital, the removal resulting in "cachexia thyreopriva"; (2) by the experimental prevention of such a condition by the use of thyroid grafts or the administration of thyroid substances (Schiff); (3) by the theory definitely advanced by Möbius[8] that "Graves' disease is an intoxication of the body by a morbid activity of the thyroid gland."

Clinical and pathologic studies now began to include more detailed descriptions of the anatomic changes in the thyroid gland, the former discussions of which were often incidental to dissertations on the pathologic anatomy of other organs and tissues believed at that time to be primarily basic in the production of the symptoms of exophthalmic goiter. In the light of the contribution of Möbius, various gross characteristics of the morbid anatomy were pointed out. Clark[9] spoke of a diffuse primary hypertrophy followed by a shrinking of the gland after death. He described the gland as firm, vascular and fleshy. Bogrow[10] and Baldwin,[11] who made similar observations, also concluded that there was a primary hypertrophy followed by a secondary atrophy. Such diffuse enlargements were confirmed in a general discussion lead by Murray[12] and others.[12] Askanazy,[13] Booth,[14] and Dinkler[15] pointed to the greater frequency of enlargement and involvement of the right lobe, a condition which had been observed many times before in earlier accounts. Hämig[16] discussed instances of massive involvement with diffuse accumulations of colloid. Other similar observations of colloid states were recorded in numerous surgical and postmortem studies of the glands. Notable among such observations is that quoted by Simmonds,[17] who said that while deficiency of colloid of the thyroid

7. Kocher: Arch. f. klin. Chir. **29**:254, 1883.
8. Möbius: Centralbl. f. Nervenh. u. Psychiat. **10**:25, 1887.
9. Clark: Bristol Med.-Chir. J. **5**:17, 1887.
10. Bogrow: Neurol. Centralbl. **14**:13, 1895.
11. Baldwin: Lancet **1**:145, 1895.
12. Murray: Brit. M. J. **2**:893, 1896.
13. Askanazy: Arch. f. klin. Med. **1**:118, 1898.
14. Booth: New York M. Rec. **54**:217, 1898.
15. Dinkler: Arch. f. Psychiat. **33**:2, 1900.
16. Hämig: Arch. f. klin. Chir. **55**:1, 1897.
17. Simmonds: Schmidt's Jahrb. **234**:134, 1892.

gland was the rule, not infrequently it was of normal or increased colloid content. These conclusions were in opposition to the views by Farner,[18] Müller,[19] Edmunds,[20] Kraus,[21] Sellerier[22] and Haskovec.[23] These authors were in agreement with the prevailing conception, namely, that the thyroid of "exophthalmic goiter" manifests itself as a compact, fleshy, vascular, granular, colloid-deficient gland, usually with a diffuse involvement. In addition to such changes nodules and cysts were reported found in the glands in scattered instances.

Microscopic changes varied with the gross observations. In general, it was observed that there was a widening out of the acini with a marked tendency to papillary formation, a columnar type of epithelium, a diminution in the colloid, a relative reduction in the supportive connective tissue, an infiltration with round cells and an increased vascularity with engorgement. Those who observed a richness of colloid contended that this substance predominated. Simmonds,[17] who opposed this latter view, stated that he observed a change in the staining of the colloid in two thirds of his cases, a papillomatous hyperplasia in half of them and desquamation in one fourth. He concluded that the irregularity was functional and not bound to any anatomic type. Hezel[24] pointed out that the process could not be considered hyperplastic, but must be viewed as adenomatous. The vascularity, the infiltrations with round cells and the necrotic areas appeared to him as an inflammatory process. Ehrich[25] observed a spotty formation of mucin in newly formed acini. Horsley[26] noted the formation of secretory vacuoles in the epithelial cells. In those glands in which he observed nodular and cystic changes, he found deposits of lime salts and fibrosis.

Möbius,[27] in his monograph on "Die Basedowische Krankheit," summarized his observations on the pathologic anatomy of the thyroid previous to 1900 as follows: "It appears that Basedow's symptoms may be observed in all types of goiter, large and small, hard and soft, with and without cysts and probably in malignant tumors of the gland." He remarked further that if a normal gland existed prior to the onset of the disease, a soft goiter of moderate size, usually larger on the right than on the left side, resulted. The other gross and microscopic changes he regarded as preexisting structures to which the changes induced by

18. Farner: Arch. f. path. Anat. **143**:509, 1896.
19. Müller: Beitr. z. path. Anat. u. z. allg. Path. **19**:127, 1896.
20. Edmunds: J. Path. & Bact. **3**:488, 1894.
21. Kraus: Buffalo M. J. **35**:793, 1896.
22. Sellerier: Thèse de Paris **255**:138, 1897.
23. Haskovec: Schmidt's Jahrb. **258**:127, 1898.
24. Hezel: Deutsche Ztschr. f. Nervenh. **4**:4, 1893.
25. Ehrich: Beitr. z. klin. Chir. **28**:1, 1900.
26. Horsley: Brit. M. J. **2**:1623, 1896.
27. Möbius: Specielle Path. u. Therap., Nothnagel **22**:18, 1896.

exophthalmic goiter were added. During the next twelve years painstaking experimental, clinical and anatomic studies of goiter, in general, tended firmly to establish the basic rôle of the thyroid in hyperthyroidism. Adherents of the "neurogenic theory" of the causation of exophthalmic goiter continued occasionally to advance pathologic evidence in support of their convictions, but their dissertations failed to stem the tide of studies concerning the relationship of disorders of the thyroid to clinical phenomena associated with its hypersecretion. A greater attempt was made to analyze the different clinical types and to correlate them with pathologic changes in the thyroid. Kocher [28] divided the instances (seventy-nine) in which operation was performed in the clinic of Kocher into the following groups: thirty-seven, high grade exophthalmic goiter; twenty-two, definite exophthalmic goiter with some symptoms missing; fourteen, strumae vasculosae; two, pseudo-exophthalmic goiter, and four, unclassified. In all of these instances the glands were enlarged. The older ones were more firm. Variable types of structure with no marked colloid or nodular types were found grossly and microscopically. Murray,[29] in citing his observations in a number of instances, mentioned four in which hyperthyroidism occurred in the presence of unilateral enlargement with adenoma or cystadenoma.

Histologic studies of the various types of glands in hyperthyroidism now began to be especially emphasized, since up to this time many of the gross characteristics had been more widely observed. Erdheim [30] reviewed and analyzed the more important studies and quoted the following authors and their concepts: (1) Brissand, a thyroid affected but without specific change; (2) Müller, specific cell hyperplasia and stroma, but still a colloid struma; (3) Farner, long follicles, papillary growth and cylindric epithelium; (4) Hämig, parenchymatous hyperplasia, solid cell masses, enlarged follicles and a colloid type in which the typical hyperplasia could not occur; (5) Askanazy, Hämig's effect of colloid, desquamation of cells and an excessive accumulation of connective tissue that shut off the lymphatic drainage and forced the "unripe poisonous thyromucin into blood vessels"; (6) Ehrich, an adherent of the vasoneural theory—a papillary structure to be regarded, as a phenomenon of coalescence, and (7) Langhans, irregularity of epithelium as the most important observation, possibly an increase, decrease or modification of colloid and probably a chemical alteration of secretion. Erdheim in a detailed careful study of a number of glands laid stress on the necessity of differentiating the young from the old cells by a method involving the staining of fat granules with osmium tetroxide, a

28. Kocher, Albert: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9**:1, 1902.
29. Murray: Lancet **2**:1194, 1902.
30. Erdheim: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.

technic which he had previously applied in differentiating adenoma from adenocarcinoma. He concluded (1) that in definite exophthalmic goiter there is a lively development of new formations, (2) that the new follicles may be large with papillae or small with flattened walls, (3) that many of the small cell masses are old and represent follicles that have degenerated through desquamation, (4) that different types of cells may be found in other types of struma, but in exophthalmic goiter the cells are young as determined by the granules, (5) that in addition to these typical changes follicles in which the colloid has degenerated and cysts may occur and (6) that the presence of fat cells in the supportive stroma is physiologic and not alone a matter of nutrition. He thought that the retrogressive changes probably indicate that the increased activity is superimposed on previous disturbances of the thyroid.

Wilson [31] in a clincopathologic study of 294 instances (operations and autopsies) divided them into two series with four groups in each. In the first series, he included all those types that were regarded as having the initial disturbance in the thyroid, as follows:

1. Eleven cases. The patients were young women with symptoms of from two months' to two years' duration. The thyroid glands were hard and granular and of an average weight of about 30 Gm. The cut surfaces were dry, granular and vascular. Microscopically, the chief characteristics seen in all of them were an increased number of cells with reduplication and a small amount of noneosin-staining secretion.

2. Nine cases. The patients were females, and all presented the classic symptoms. The glands weighed, on the average, about 53 Gm., and were hard, nodular and granular. Microscopically, the chief changes were papillary formations, infolding, large interalveolar increase of parenchyma and large amounts of noneosin-staining substance.

3. Fourteen cases. The patients were females and had had the symptoms for from three to thirty years. The essential microscopic characteristics were large intra-alveolar increase of parenchyma with a greater number of cells in a single layer, reduplication of layers and a large amount of thin secretion.

4. Thirty-four cases. All of these were regarded as in the second and third clinical stages. The essential histologic changes were an increase of stroma, an old intra-alveolar increase of parenchyma, the remains of infolding and a large amount of eosin-staining secretion.

In the second series, secondary changes in the gland were observed. Wilson concluded that the symptoms of exophthalmic goiter are asso-

31. Wilson: Am. J. M. Sc. **136**:851, 1908.

ciated with an increased absorption of an increased secretion; that the larger the number of functioning cells, the greater the secretion; that the more fluid the secretion, the more readily is it absorbed; that dense colloid is probably no evidence of present secretion but the complement of the absorbed portion, and further, that there was evidence of blocked absorption.

Shepherd and Duval,[32] in a study of fifty-nine cases, concluded that no etiologic changes could be regarded as specific for any special type of disease of the thyroid gland. Beck [33] presented another view stating that in simple goiter there is an abnormal increase of normal thyroid tissue and that hypertrophy may be either nodular, diffuse, parenchymatous, colloid, fibrous or vascular. He explained the increased activity on the basis of multiplication of the follicles, an increase of their contents and an associated increase in their vascularity.

Simmonds,[34] in a study of 100 instances of exophthalmic goiter, commented on the minute structural changes as follows: The colloid was diminished in two thirds of the specimens and normal or increased in the remainder. Follicular papillary epithelial hyperplasia and polymorphism of the alveoli were found in one half of the number. The presence of this change he regarded as diagnostic, the absence as of no significance. Desquamation of the epithelium was present in one fourth of the specimens, but this also occurred in acute infections. The hyperplasia of the lymphoid follicles (in 80 per cent of the cases) was a true response to a pathologic secretion; it was not of the inflammatory type. In the 80 per cent of the instances in which it was found, 84 per cent of the patients had symptoms of typical exophthalmic goiter while the other 16 per cent presented an atypical symptomatology. Simmonds further concluded that exophthalmic goiter is a symptom complex with no fixed pathologic picture in the thyroid gland.

While these careful observations were analytic, they did not satisfy the constant demand for a more accurately utilizable classification. Marine and Lenhart [35] attempted this in an interpretation of the structural changes in the hyperplasias of the thyroid. These authors divided such conditions into primary and secondary manifestations, as follows:

Primary (seventeen cases): (*A*) Developmental Stage: Grossly, in the classic type, the gland was larger, softer and a brighter red. Microscopically, it showed a lessening of the stainable colloid, vacuolization resulting in a granular débris and the formation of high cuboidal epithelium. Later, the gland became gray-red and finally

32. Shepherd and Duval: Tr. Am. Surg. A. **27**:56, 1909.

33. Beck: New York M. J. **91**:937, 1910.

34. Simmonds: Deutsche med. Wchnschr. **37**:2164, 1911.

35. Marine and Lenhardt: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265 (Sept.) 1911.

changed from soft gray-red to grayish opaque, with infolding and increase of connective tissue as the cytologic changes. The glands remained symmetrical and rarely exceeded 200 Gm. in weight. (*B*) Involutionary Recovery or Colloid Stage: The gross and microscopic changes consisted of a reversal of those observed in group A. (*C*) The Stage of Exhaustion or Premature Atrophy: Grossly, the gland was smaller and firmer to the touch, granular and of a reddish opacity. The vascular increase remained. The increase of stroma was evident with false lobulation, but colloid was not seen. Microscopically, the acini were pressed by the increase in the connective tissue, with cell masses included. The epithelium was of a uniform high columnar type with a failure to form follicles. Desquamation, hyperchromatic nuclei and mitotic figures were also noted. In comment on the general changes in primary hyperplasia, Marine and Lenhardt pointed out that "the thyroid undergoes exceedingly rapid changes within the limits of health and disease, and further that excessive hyperplasia with hypersecretion unchecked will lead to cell death and in the end-stage to myxedema, and (in children) to developing cretinism with the clinical replacement of the symptoms of exophthalmic goiter by those of myxedema."

In the group of the secondary hyperplasias (twenty-six cases) were placed the active hyperplasias that were thought to have developed from a colloid gland. The essential anatomic changes were similar to those of the primary hyperplasias. Another group presented evidence of hemorrhage, degenerations, tumors and cystic formations, all of which the authors concluded, may modify the adjacent tissues. The stage of exhaustion was similar to that of the first stage in the primary hyperplasia. The pathologic changes described by Marine and Lenhardt were similar to those mentioned briefly by Kocher,[36] who attempted to correlate the exact clinical symptomatology with the cytologic changes and the iodine content of the gland.

Plummer [37] began to evaluate the mass of data that had accumulated, and from studies of his own concluded that exophthalmic goiter is a definite clinical complex associated with a hyperplasia of the thyroid gland that is proportionate to the degree of toxicity (toxic hyperplastic), and that it should be sharply differentiated from the constitutional states that may develop with nonhyperplastic goiter. Wilson [38] corroborated the opinion of Plummer in a detailed study of the thyroid in these different conditions. He also pointed out that many mild cases of toxic goiter reported in the literature have apparently been classed as simple goiter. Wilson further mentioned two divisions of such milder types, namely, class I, hypertrophies, hyperplasias and

36. Kocher, A.: Arch. f. klin. Chir. **95**:1007, 1911.
37. Plummer: Am. J. M. Sc. **146**:790, 1913.
38. Wilson: Tr. A. Am. Phys. **28**:576, 1913.

regenerations (79 per cent); and class II, fetal and colloid adenomas, adenomatoses and simple colloid goiter (21 per cent). The degree of toxicity could be determined, according to Wilson, from the structural changes with 80 per cent accuracy. Thus, in the numerous records of these investigations there were being slowly evolved criteria of the basic changes in hypersecreting or malsecreting thyroid glands in persons with variable symptoms.

Warthin,[39] in a recent report on 976 resected glands, 30 glands taken at autopsy from patients who had died following operation for exophthalmic goiter and 1,000 thyroid glands from autopsies on other persons, called attention to the existence of lymphoid tissue in connection with the many different structural changes of the thyroid gland in exophthalmic goiter. He concluded that the thymicolymphatic constitution underlies every case of exophthalmic goiter.

When one reflects on the great number of articles that have contributed to knowledge of the pathologic anatomy of the thyroid associated with its hyperactivity, one finds that there has developed a rather definite clinical picture and concept of the gross and microscopic aspects of the so-called classic type of thyroid in exophthalmic goiter. There is a uniformity of supporting evidence that: (1) the gland may vary in size from a very slight to a moderate degree; (2) it is symmetrically enlarged, with the possibility of the right lobe being somewhat larger than the left; (3) there is little accentuation of the lobular markings; (4) the capsule and supportive stroma are little, if at all, increased, (5) the structure of the gland may be vascular or ischemic, if the hyperplasia is marked, (6) the colloid is not grossly visible, (7) the color ranges from pinkish to opaque gray, depending on the intensity of the hyperplasia and the relative vascularity of the gland and (8) it is fleshy and moderately firm. Microscopically, there is observed: (1) a patchy increase in the fibrous connective tissue of the supportive stroma, (2) engorgement of the arteries and veins and dilatation of the lymphatic channels, (3) a variable infiltration with round cells, (4) polymorphism of the alveoli, (5) hyperplasia of the epithelium and hypertrophy with variable infolding and (6) diminution of the colloid with variation in its character. Although there have been many conflicts of opinion as to the significance and value of these different gross and microscopic manifestations, there is an obvious unanimity of the understanding of this specific response of the thyroid in the excess fabrication of its essential substance.

In addition, there has also been evolved another mass of convincing evidence that the thyroid gland does not always respond to stimuli in

39. Warthin: Ann. Int. Med. **2**:553, 1928.

this typical classic manner. The citations from the literature to this point indicate that normally the thyroid has a fluctuating physiologic response, the imprints of which may be left in the form of accidental structural modifications that react differently to subsequent stimuli. Under such condtions, a markedly variable clincal and structural response might be expected. Almost paralleling the records of classic examples of exophthalmic goiter are those of atypical manifestations. Interesting studies had been made, and more were to follow in the next thirteen years.

The recognition by Oswald (1899, 1908, 1909) that the activity of the thyroid is confined to its iodine-containing colloid, thyroglobulin, eventually led to the discovery of thyroxin by Kendall (1914). Following this, pertinent observations were made by Plummer,[40] whose presentation of the clinical differentiation between exophthalmic goiter and adenoma with hyperthyroidism served as a stimulus to further segregation of clinical types and the study of the pathologic anatomy of the thyroid gland underlying them. Plummer recorded the following facts as important: 1. There is a previous enlargement in cases of adenoma of the thyroid. 2. The time elapsing between the enlargement and the onset is fourteen and a half years in instances with adenoma and only nine tenths of a year in cases of exophthalmic goiter. 3. Exophthalmos is absent in hyperthyroidism from adenoma. 4. Hypertension and myocardial disease is more frequent in cases of adenoma. 5. Seventy-seven per cent of the patients with adenoma are more than 40 years of age, while those with exophthalmic goiter average 35 years of age. 6. The basal metabolic rate drops rapidly after the removal of an adenoma and slowly after the removal of the thyroid tissue in exophthalmic goiter.

In 1916, Goetsch,[41] who regared adenoma as a new growth of benign nature with colloid, cystic and fetal types, studied these types with a view to establishing their rôle in the production of toxic symptoms Employing the technic of Bensley,[42] he observed that the adenomas contained more mitochondria than could be found in the surrounding tissue; and as further evidence of their ability to hypersecrete, he recorded the abatement of symptoms following their surgical removal. Lahey [43] agreed with Goetsch, concluding that while nearly all the cells of the gland took part in the activity of the primary hyperthyroidism, only those in the adenoma were active in secondary hyperthyroidism. In the succeeding years, much clinical and pathologic evidence of the

40. Plummer: Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, J. A. M. A. **61**:650 (Aug. 30) 1913.

41. Goetsch: Bull. Johns Hopkins Hosp. **27**:129, 1916.

42. Bensley: Am. J. Anat. **19**:37, 1916.

43. Lahey: Internat. Clinics **4**:65, 1917.

rôle of adenoma was recorded in the literature. Jackson [44] observed instances of toxicity with multiple adenoma in the glands. Wilson [45] discussed "nodular goiters" with and without symptoms of hyperthyroidism. He divided them into two groups according to the basal metabolic rate. Shepard [46] was of the opinion that the pathologist is unable to distinguish between an adenoma causing hyperthyroidism and one which is inactive. Hertzler [47] looked on the occurrence of adenoma as an incident in the changing structure of the gland as it progresses through the period of adolescence. He concluded that the whole gland is diseased. Rienhoff [48] in a study of involution or regressive changes divided them into spontaneous involutions and hyperinvolutions. He observed the formation of nodules in regressions of the glands of exophthalmic goiter, and further pointed out that "areas of hyperinvolution correspond clinically and histologically to the so-called colloid adenomas, cystadenomas, fetal and colloid or mixed adenomas and colloid cysts." I [49] observed conditions in adenoma similar to those found by Hertzler and Rienhoff. More recently, Rienhoff and Lewis [50] analyzed 109 instances of nodular goiter with symptoms of hyperthyroidism in comparison with the changes in the remissions of exophthalmic goiters undergoing treatment with iodine. They pointed out that there is a striking similarity in structure between the iodine-treated glands and nodular goiter. They further concluded that "the nodules or involutional bodies are not neoplasms in any sense of the word but are merely regressive sequelae of a previous hypertrophy and hyperplasia of the parenchyma." They further stated that there is no proof of the existence of a hypersecreting neoplasm. Hertzler [51] held similar views; namely, that the diseases of the thyroid gland must be viewed as a continous process. Thus the nature and origin of these benign so-called adenomas have been discussed at length from the standpoint of the conflicting views of Wolfler,[52] who regarded them as originating in interacinar embryonic cell rests, and that of Virchow, who considered them (except fetal

44. Jackson: Wisconsin M. J. **21**:461, 1923.

45. Wilson: Am. J. M. Sc. **165**:738, 1923.

46. Shepard: California State J. M. **21**:16, 1923.

47. Hertzler: Endocrinology **10**:175, 1926.

48. Rienhoff: Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter and Their Relation to the Origin of Certain of the So-Called Adenomas, Arch. Surg. **13**:391 (Sept.) 1926.

49. Menne, F. R.: Northwest Med. **26**:304, 1927.

50. Rienhoff and Lewis: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928.

51. Hertzler: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. **16**:61 (Jan.) 1928.

52. Wolfler: Arch. Chir. **29**:1, 1883.

adenomas) solitary or multiple nodular accumulations originating from a preexisting thyroid pattern. Cline,[53] in a study of 600 instances, concluded that the structural evidence observed by him substantiated the concept of Virchow. Their ability to produce an excess of hormone has never been conclusively proved. Many of the studies seem to indicate that while they may become active and hypersecrete, there is usually enough evidence in the surrounding structure of the gland as a whole to explain the symptoms occurring in a given instance.

During the time that attention was fixed on the importance of nodule formation, allied microscopic structural changes were being analyzed as to their significance in hypersecretion. In 1922, Goetsch [54] called attention to a focal interstitial formation of new acini, which he designated as adenomatosis, and pointed to its being a factor in mild hyperthyroidism. Helwig,[55] in a well illustrated study, pointed to the existence of small, disseminated hyperplasias in the form of interalveolar and intra-alveolar collections of acini with characteristic cellular changes as being responsible for the production of "hyperthyroidisms of the lighter grades." Helwig [56] further traced the steps of development from a simple colloid goiter to a typical exophthalmic type. Holst [57] made similar observations, concluding that changes in primary hyperthyroidism begin as a local proliferation. This further complicated the attempts to establish a definite structural change in the thyroid gland that may be associated with a given clinical picture. One is forced back to the necessity of applying the gross and microscopic criteria of the activity of the thyroid in classic exophthalmic goiter to the many intricate complexities of structure that present themselves for solution. A résumé of the literature leads one to the conclusion that specific clinical classifications of the types of hyperthyroidism are as futile as detailed classifications of the types of nephritis, when one tries to make the whole thyroid gland conform in structure to a fixed set of physiologic irregularities in different persons.

Although there have been conflicting interpretations of the thyroid in health and disease, there are outstanding facts of common observation. It is generally agreed that the gland varies markedly in size and shape and that clinically the picture ranges from cretinism and myxedema to hypersecretion of dysfunction as the case may be. We [58] have been able to group the surgically removed portions or entire glands

53. Cline: Am. J. Path. **1**:235, 1925.
54. Goetsch: Endocrinology **6**:59, 1922.
55. Helwig: Beitr. z. klin. Chir. **125**:75, 1922.
56. Helwig: Deutsche med. Wchnschr. **48**:420, 1922.
57. Holst: Acta. chir. Scandinav. **4**:191, 1923.
58. Menne, F. R.; Joyce, and Von Hungen: Thyroid Disturbances: Clinicopathologic Study of Three Hundred Instances, Arch. Surg. **13**:329 (Sept.) 1926.

according to their gross pathologic characteristics and predominating microscopic pathologic structures as follows:

I. Diffuse parenchymatous hyperplasia—marked increased activity
   (1) Gross observations: Gland compact, vascular or ischemic, grayish to pinkish white and colloid-free
   (2) Microscopic observations:
      (*a*) Hyperplasia and hypertrophy of epithelium
      (*b*) Peripheral or general vacuolization of colloid
      (*c*) Dilatation of lymph channels and engorgement of blood vessels
      (*d*) Variable increase in the supporting stroma with or without round-cell infiltration

II. Disseminated adenomatous hyperplasia—normal or moderately increased activity or no activity
   (1) Gross observations: Gland diffusely reddish-brown without noticeable nodularity or accentuation of lobular markings; a variable amount of colloid and pinkish to yellowish gray opacities
   (2) Microscopic observations:
      (*a*) Focal changes similar to those in group I
      (*b*) Normal or colloid-distended alveoli
      (*c*) Focal hyperplasia and hypertrophy of epithelium
      (*d*) Interalveolar hillocks or intra-alveolar papillomatous projections
      (*e*) Focal collections of round cells or pseudolymphnodes
      (*f*) Focally increased vascularity and dilated lymph channels
      (*g*) Focal fibrous increase of connective tissue

III. Nodular adenomatous hyperplasia—subnormal, normal or moderately increased activity
   (1) Gross observations: Variable nodular accentuation of the lobular markings with or without excessive storage of colloid cystic degeneration, hemorrhage, scarring or deposit of lime salt. The color usually varies with the regressive changes
   (2) Microscopic observations:
      (*a*) Focal changes similar to those found in groups I and II and compensatory
      (*b*) Characteristic retrogressive changes
      (*c*) Areas of adenomatosis

IV. Solitary adenoma
   (1) Gross observations: Adenoma variable in size, circumscribed, solitary or multiple, grayish-white to dark reddish-brown, solid and cystic or colloid-filled. Regressive changes may be present.
   (2) Microscopic observations:
      (*a*) All stages of fetal types of alveoli
      (*b*) Peripheral formation of pseudocapsule with round cell infiltration and compressed alveoli
      (*c*) Focal hyperactive areas in adjoining parenchyma
      (*d*) Adjacent areas of adenomatosis

While the gross division of the portions of the thyroid removed is rather easily affected according to this outline, there are numerous instances of the shading of one group into another. Glands of border line nature may, for the sake of study, be relegated to the group

according to the dominancy of the classifying characteristics. More detailed separations of types of disturbances seem futile.

In the microscopic analysis, it is important to establish histologic criteria of activity or rest. One thing is certain; namely, that the histologic appearance of the gland in group I (diffuse parenchymatous hyperplasia, so-called classic exophthalmic goiter) is just as definite as are the gross and clinical manifestations associated with it. This is conceded to be an entity in all respects. One may therefore safely assume that the microscopic pattern found here is that resulting from the production and delivery of thyroid hormone or its by-products into the lymphatics or veins. There is evidence to show that cellular hypertrophy, hyperplasia, peripheral vacuolization of colloid, dilated lymph channels and veins and the resulting alveolar distortion occur in the order named and are natural steps in the mechanism or function of any ductless gland and that they are accompanied by an increased blood supply to the part. Prolonged activity probably leads to the necessity for more supportive stroma, and the appearance of special inflammatory absorption reactions consisting of collections of lymph cells. Finally, destruction with areas of adenomatosis or a gradual reversal of the process occurs.

Any pathologic classification from a practical point of view is of value only so far as it may be readily fitted into a specific clinical concept. It has been of interest to note that there are many difficulties in such an assorting of thyroid diseases, and that the situation approaches futility when there is an attempt made to give each detail in the morbid anatomy a distinctive entity. Until more exact physiologic knowledge is at hand, the clinician and the pathologist must content themselves with a comparison of the evidences of disease in the patient and the anomalies of thyroid design as seen in the laboratory. The object in presenting this grouping is to show the extreme range of pathologic structure of the thyroid gland that one may find associated with the production of substances leading to so-called hyperthyroidism. In the case of every type represented, the clinical evidences of hyperthyroidism were found. The greater number of instances of classic types were found in the first two groups, but in all the groups were glands of patients who presented all of the typical symptoms of exophthalmic goiter. All gradations from the milder to the more severe forms of hyperthyroidism were found occurring as the result of the types of glands considered.

It seems from the literature that careful cytologic study of any given gland of a patient with clinical evidence of hypersecretion of the thyroid results in the disclosure of minute structural changes adequate to explain the degree of toxicity. Such specific microscopic foci may be entirely masked by the gross retrogressive structural changes of the gland at the time it is removed for study. It furthermore appears

from the conclusions of numerous other investigators that the general trend of opinion conforms to this.

THE INFLUENCE OF IODINE ON HYPERSECRETION OF THE THYROID GLAND

After more than a century of familiarity with the isolation and identification of iodine (Coindet, 1820) and a growing knowledge of its natural distribution in plant and animal life, its agency in the physiology of the latter, and of man in particular, is as yet not thoroughly understood.

In the accounts of medical practices of many centuries past are records of the use of iodine-containing substances in many ailments and especially in goiterous enlargements of the neck. Its use in the latter condition gradually became rationalized (1) by the determination of the presence of iodine as a natural constituent of the thyroid gland (Baumann, 1895), (2) by the experiments of Marine and Lenhardt, who protected animals (dogs and fish) from goiterous enlargements by the addition of the required amount of iodine to their food, (3) by the further experiments of these two authors [59] on regeneration and hyperplasia in the thyroid as influenced by iodine, (4) by the isolation and identification of thyroxin as the active principle of the thyroid (Kendall, 1914) and (5) by the observations of Plummer and Boothby concerning its clinical use in hyperactivity. To these might be added many other similar experiments and studies all of which pointed to the specific rôle of iodine in the physiology of the thyroid in health and disease.

While these important advances relative to the identification of iodine as a positive and necessary factor in thyroid functioning were developed, many clinical observations were also made with a view to a better understanding of the empiric use of iodine in thyroid irregularities. As a remedial agent in so-called goiter, iodine had been used in its crude form (ashes of sponge or seaweed) for many thousands of years. The purification of iodine and its compounds led to more accurate dosage and the development of various means of administration. The results were not wholly satisfactory because of the lack of control of clinical conditions and the inability of early clinicians accurately to differentiate the different types of thyroid disease. But from the time of the establishment of exophthalmic goiter (1786) as an entity, it was considered unwise to use iodine in the therapy of this condition. Occasionally, however, on account of erroneous diagnoses or by accident, iodine was administered and beneficial results were noted.

59. Marine and Lenhardt: Relation of Iodin to the Structure of Human Thyroids, Arch. Int. Med. **4**:440 (Nov.) 1909.

Trousseau [60] (1863), by mistake, gave tincture of iodine instead of tincture of digitalis to a patient with a supposed cardiac irregularity, which was probably secondary to hyperthyroidism. Improvement of the patient was noted and recurrence of the symptoms was observed when the correction was made. Numerous other instances of the beneficial uses of iodine in so-called exophthalmic goiter were recorded, but in general the results were bad, and in many of the large clinics of Europe the use of iodine in this disease fell into disrepute. But surgical removal in primary hyperthyroidism gave a mortality rate so high that frantic efforts were constantly being made to better the technic and to find further aids in the therapy. The introduction of rest in bed, the isolation of clinical types, the use of soporifics and preliminary pole ligations helped appreciably to lower the mortality rate. In the meantime the effect of partial surgical removal on the remaining gland stump was studied by Wagner,[61] Horsley [62] and Halstead,[63] who found that reconstructive hyperplasia and hypertrophy occurred. This observation led to a further understanding of what surgical removal accomplished besides the mass removal of offending parenchyma. It also opened the way for a study of the additional effect of iodine as a therapeutic adjunct.

During the succeeding years many attempts were made to use iodine in instances of hypersecretion, but its effects were too variable and often too dangerous. Its ultimate efficacy was to be dependent on further observations. Kocher [64] referred to the marked reduction of the amount of iodine associated with deficiency of colloid in the glands with marked hyperplasia in hyperthyroidism. Later Marine [65] pointed out that in 137 cases of exophthalmic goiter in which operation or autopsy had been performed, no specific anatomic changes were found; that the iodine content varied directly with the degree of active epithelial hyperplasia; that the administration of iodine in the simple hyperplasias of the thyroid in man and animals is followed in from three to five weeks by a progressive involution of the hyperplasia to its colloid stage. These experiences were confirmed by Kocher and others, who began to observe the effect of the feeding of iodine to exophthalmic patients as having a result that would substantiate this particular influence of iodine. Lowey and Zoudek [66] found that the use of iodine in primary

60. Trousseau: Clinical Lectures, translated by Bazire, London, New Sydenham Society, 1868, vol. 1, p. 587.

61. Wagner: Wien. med. Bl. **7**:771, 1884.

62. Horsley: Lancet **2**:1163, 1886.

63. Halstead: Johns Hopkins Hosp. Rep. **1**:373, 1898.

64. Kocher: Arch. f. klin. Chir. **95**:1007, 1911.

65. Marine: Anatomic and Physiologic Effects of Iodin on the Thyroid Gland of Exophthalmic Goiter, J. A. M. A. **59**:325 (Aug. 3) 1912.

66. Lowey and Zoudek: Deutsche med. Wchnschr. **47**:1387, 1921.

hyperthyroidism tended to bring the basal metabolic rate back to a normal level. Plummer, having in mind the possible toxicity of incompletely iodinized thyroxin and the variations in the symptomatology of the clinical types, suggested that the administration of a compound solution of iodine in instances of primary hyperthyroidism might be of value. Subsequently, Plummer and Boothby [67] published the beneficial results of its use in selected cases. Similar reports by others began to appear. Starr and Segall,[68] in a study of forty-two cases, made additional observations. They determined that the rate of detoxification (based on the reduction per diem in the basal metabolic rate) was 3.7 points, a rate similar to that obtained by Means and Aub [69] with subtotal thyroidectomy alone. They further pointed out that in 48 per cent of these cases, the administration of iodine had the same effect on the basal metabolic rate as the removal of five sixths of the gland; that iodine did not produce permanency of remission, recurrence being the rule, and that the return of intoxication resulted in a much higher basal metabolic rate. They therefore concluded that no gap should be allowed between the therapy employing iodine and the operation. This conclusion was concurred in by Chute,[70] who regarded the "optimal time" for thyroidectomy to be within a period of from two to three weeks after the treatment with iodine was started. During this time he observed the most marked clinical improvements and the greatest drop in the basal metabolic rate. He regarded the operation within such a time limit as safe, and also stressed the fact that the toxicity recurring after cessation of the treatment with iodine is greater than before its use, if surgical removal is not promptly made. He further concluded that in the severe cases iodine reduced the necessity of pole ligations from 51 to 13 per cent, but that iodine, even though administered over a long period of time, does not cure exophthalmic goiter. Petren [71] regarded iodine as having a life-saving action. He also noted that the symptoms reappeared after cessation of the treatment and recommended the use of roentgen rays and ligation as additional measures.

Marie [72] concluded that the results of the use of iodine testify only that a disproportion exists between the iodine content and the requirement of the organism at the time rather than a deficiency of iodine. Marine [73] later called attention to the use of iodine in too large

67. Plummer and Boothby: J. Iowa M. Soc. **14**:66, 1924.

68. Starr and Segall: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.

69. Means and Aub: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917.

70. Clute: The Effect of Compound Solution of Iodin and Rest in Surgery of Exophthalmic Goiter, J. A. M. A. **86**:105 (Jan. 9) 1926.

71. Petren: Ugesk. f. Laeger. **88**:363, 1926; abstr., J. A. M. A. **87**:72, 1926.

72. Marie: Presse méd. **34**:580, 1926.

73. Marine: Ann. Clin. Med. **5**:942, 1927.

amounts (compound solution of iodine contains 125 mg. of iodine per cubic centimeters). It was suggested by him that smaller amounts more nearly physiologic (1 mg. daily) should be given. He spoke of the preoperative measure of "heroic doses" as dangerous, from which much harm had occurred and would continue to occur. Marine regarded the beneficial effects of iodine in exophthalmic goiter as limited and its injurious effects as serious. He also stated that these injurious effects had increased during the last three years and were more serious than the disturbances noted as a result of the preventive use of various iodine-containing substances. Marine explained the effect of iodine on the basis of a probable storage of colloid which holds back secretion. He stated that when secretion is released, it is reestablished with full force and yields larger amounts, the gland becoming larger and more solid. Helwig's [74] views were in agreement with those of Marine. He concluded that the feeding of iodine called forth an enlargement of the follicles and a thickening of the colloid, and stated that in his experience the severest cases of exophthalmic goiter were encountered after the administration of iodine.

Sager [75] again called attention to the necessity of differentiating the types of hyperthyroidism before beginning the use of iodine, on the basis of Plummer's views. He quoted Plummer as regarding the action of iodine as due to one of three possibilities: (1) complete iodinization of thyroxin in the tissues (possible but improbable); (2) complete iodinization of thyroxin in the thyroid (most probable); (3) blocking of the discharge of the hormone.

More definite observations on the structural changes in the thyroid now began to appear (Cattell,[76] Warthin,[77] Giordano,[78] Kaffler,[79] Marine,[80] Helwig,[81] Sager,[75] Rienhoff and Lewis,[50] Menne, Joyce and Stewart [82]). All these studies agree that the essential changes induced by iodine consist of a regression of activities with an accumulation of colloid, a reduction in the degree of hyperplasia and hypertrophy of the epithelium and a decrease in the vascularity. Grossly, the glands tend to become larger, on the average, than untreated glands. The capsule and supportive stroma are not appreciably altered unless considerable

74. Helwig: Klin. Wchnschr. **5**:2356, 1927.

75. Sager: Exophthalmic Goiter: Pathologic Changes as a Result of the Administration of Iodine (Lugol's Solution), Arch. Surg. **15**:878 (Dec.) 1927.

76. Cattell: S. Clin. N. Amer. **6**:597, 1926.

77. Warthin: Ann. Clin. Med. **4**:686, 1926.

78. Giordano, A. S.: Histologic Changes Following Administration of Iodine in Exophthalmic Goiter, Arch. Path. **1**:881 (June) 1926.

79. Kaffler: München. med. Wchnschr. **73**:1400, 1926.

80. Marine: Ann. Clin. Med. **5**:942, 1927.

81. Helwig: Klin. Wchnschr. **5**:2356, 1927.

82. Menne, Joyce and Stewart: Ann. Int. Med. **1**:912, 1928.

time elapses during the therapy. Colloid is visible, and spotty, yellowish gray to pinkish gray opaque areas of hyperplasia may be seen. These changes are not unlike the involutional changes of untreated glands or of the types of disseminated adenomatus hyperplasias associated with hypersecretion. Although clinicians have made an attempt to utilize iodine only in nodule-free glands, occasionally nodules were found in the specimens of glands examined by us. Microscopically, the essential changes noted vary somewhat with the type of disease of the individual gland. In general, there occurs a progressive development of intracinar colloid, an ironing out of the papillary infoldings, a marked reduction in the hyperplasia and hyperthrophy of the epithelium and the development of more uniformity in the sizes of the alveoli. As a rule, the longer iodine is administered, the greater is the accumulation of colloid. But over-iodinization in the presence of the continuance of the etiologic factors of the disease not infrequently results in areas of hyperplasia and hypertrophy that break through the colloid resistance, and such areas may then hypersecrete with renewed energy. Because of this limited effect of iodine on the progression of the disease, surgical removal of a large portion of the gland in the hope of a normal rebuilding is still practiced. While the reversion in the pathologic changes of the thyroid gland induced by iodine is valuable from the standpoint of therapy, and throws light on the mechanism of internal secretion in health and in disease, the relationship of iodine to the etiology is still obscure.

SUMMARY

The earlier classifications of the pathologic anatomy of the thyroid consisted of extensive lists of anatomic terms indicating different degenerative or retrogressive processes. Such changes were often regarded as disease entities with which certain clinical phenomena could be associated. While there was this confusion in the general knowledge of thyroid irregularities, there was, on the other hand, a more definite concept of the pathologic anatomy of the thyroid in exophthalmic goiter. It is evident from the early literature that the thyroid in such instances usually retains its symmetry, is firm, vascular, free from false lobulation and scant in colloid. Microscopic studies generally agreed on the existence of a patchy increase in the supportive stroma, engorgement of the blood vessels, infiltration with round cells, marked hyperplasia and hypertrophy of the epithelium associated with alveolar distortion and reduction and modification of the colloid. This was the consensus concerning the changes in the gland in hypersecretion.

Observations of atypical gland structure associated with certain if not all the symptoms of hypersecretion gradually began to be recorded. These thyroid glands lacked symmetry; the disturbance was in either one of the lobes, the isthmus, or in the isthmus and one lobe. The patho-

logic changes were markedly variable. In some, the capsule and supportive stroma was particularly increased (interstitial thyroiditis); in others, the anatomic pattern was retained, but spotty pinkish gray areas could be seen in a background moderately rich in colloid. Still others showed a formation of pseudolobules, while others contained solitary or multiple adenomas in various stages of development or retrogression. The recognition of such a wide range of anatomic changes in the thyroid gland and their association with varying grades of hyperactivity served to narrow the division between the definiteness of the structure of the gland in hyperthyroidism, and the many other indefinitely understood structural deformities associated with its diseases. There developed a recognition of the possibility of oversecretion by focal areas often grossly hidden by major distorting pathologic processes in the thyroid.

Solitary adenoma in many of the thyroid glands occurring with symptoms of hyperthyroidism led to the conclusion that such nodules (solitary or multiple) might be responsible for the excessive or atypical production of hormone. Concerning this there developed a conflict of views (1) as to whether such nodules are neoplasms, (2) as to their ability to secrete and (3) as to their effect on the surrounding parenchyma. Glands containing nodules (adenoma?) often presented changes varying from simple unmodified colloid-filled acini to disseminated or diffuse parenchymatous hyperplasias. Accordingly, there has not been advanced any conclusive proof that such nodules are responsible for the toxic symptoms.

The therapeutic influence of iodine on the thyroid gland has been limited to such changes as it may produce in the so-called primary hyperthyroidism. Following its use, the thyroid retains its symmetry, it enlarges somewhat because of the accumulation of colloid, the vascularity is diminished, the hyperplastic areas have a spotty distribution and the colloid become visible. Microscopically, the changes are similar to those that were described previous to the use of iodine as belonging to hyperthyroidism in which disseminated foci of hypertrophy and hyperplasia were found. It has been pointed out that the changes induced by iodine are probably similar to the natural regressive processes of variable activities of thyroid gland in health and in disease. In instances in which patients were erroneously treated on the basis of having nodule-free glands, when one or more nodules really existed, no noteworthy changes were observed within the nodules. But in such cases the characteristic changes induced by iodine were observed in the surrounding affected parenchyma.

A résumé of the many views as to the pathologic anatomic modifications of the thyroid gland associated with modified activity or hyper-

secretion tends to lead to the conclusion that, in addition to the classic changes of primary, fulminating exophthalmic goiter, there are many other grades. It is further apparent that such changes as may be directly concerned with an excessive or imperfect fabrication of hormone may lie hidden or be incompletely evident because of previously formed minor or gross distortions of structure that are contributory to, but not responsible for, the malfunctioning of the thyroid.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—Henry S. K. Willis has been put in charge of the Dows Tuberculosis Research Laboratory at the Johns Hopkins Medical School, succeeding Allen K. Krause, now director of research at the Desert Sanatorium, Tucson, Ariz.

Raymond H. Goodale, formerly professor of pathology in Beirut, has been appointed pathologist to the City Hospital, Worcester, Mass., in the place of Ernst L. Hunt, who has resigned.

Claus W. Jungelblut has resigned as associate professor in bacteriology and experimental pathology at Stanford University to accept a position in the department of bacteriology in the school of medicine of Columbia University, New York.

Alfred Plaut, formerly pathologist at the Woman's Hospital, New York, has accepted the directorship of the laboratory of Beth Israel Hospital, New York.

The death has been announced of Ernest E. Glynn, formerly professor of pathology in the University of Liverpool.

Florence Rena Sabin, member of the Rockefeller Institute for Medical Research, has been given the 1928 Achievement Award ($5,000) of the Pictorial Review.

International Congress on Veterinary Medicine.—The Eleventh International Congress on Veterinary Medicine will be held in London, England, Aug. 4 to 9, 1930. The general secretary is F. Bullock, LL.D., F.C.I.S., 10 Red Lion Square, London, W. C. 1.

State Cancer Hospital.—Money has been appropriated for the construction of a state hospital in Atlanta, Ga., for the study and treatment of cancer.

Laboratory Infection with Coccidioidal Granuloma.—It is reported that Harold DeLos Chope, assistant in public health and preventive medicine in the school of medicine of Stanford University, San Francisco, has contracted coccidioidal granuloma while working with the fungus of the disease, *Coccidiodes immitis.*

Cancer Research.—Special gifts for cancer research have been made to the Johns Hopkins Hospital providing for work on the cultivation in vitro of the cancer cell, on a differential stain for the cancer cell, and for research on cancer in the laboratory of surgical pathology.

Anthropoid Station.—Yale University has received $500,000 from the Rockefeller Foundation for the establishment and maintenance for ten years of a station in Florida for the breeding and study of the anthropoid apes. This station will be part of an expanded program in comparative psychobiology, and it will be under the direction of Robert M. Yerkes, professor of psychology at Yale. Pathology is represented on the advisory board by Theobald Smith and H. Gideon Wells.

Fellowships in Pathology.—The Charity Hospital, New Orleans, offers two fellowships in pathology, extending over two years from July 1, 1930. The stipend, in addition to full maintenance, is $900 for the first year and $1,800 for the second year. These fellowships are open to senior students in accredited medical schools, and applications should be addressed to Dr. Rigney D'Aunoy, Director of the Pathological Department, Charity Hospital, New Orleans.

The Chicago Medicolegal Society.—This newly organized society now has about twenty-five members. The president is Paul G. J. Schmitt and the secretary is Eustace L. Benjamin.

American Society of Clinical Pathologists.—The ninth annual meeting of this society will be held in Detroit on June 20, 21 and 23, 1930.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

TRANSMISSION OF INTRACRANIAL PRESSURE IN HYDROCEPHALUS IN INFANCY. KENNETH D. BLACKFAN, BRONSON CROTHERS and ROBERT N. GANZ, Am. J. Dis. Child. **37**:893, 1929.

In infants, the contents of the craniovertebral cavity do not transmit pressure according to the laws governing the pressure relations when fluids completely fill rigid containers.

1. In hydrocephalus, the propagation of abruptly applied pressure of short duration from ventricle to spinal space may be essentially immediate and without decrement. In this case, the probability of widened channels between the two cavities is assumed.

2. Delay in time and decrement in intensity may be noted. This suggests patent though narrow channels. Though there is no evidence on this point, it is suggested that this delay and decrement may also occur in normal infants.

3. The propagation of pressure may be completely blocked. This means, of course, that at the time of reading, at least, a complete discontinuity of pressure exists.

In general, it is believed that the time element in the propagation of pressure is interesting, that it can be graphically recorded and that it is possible that it may be made clinically useful. Certainly, the reliance on isolated measurements of spinal fluid pressure, as indicating intracranial pressures, seems likely to lead to serious error, and the application of the "closed box" theory to infants seems entirely unsound.

AUTHORS' SUMMARY.

DEGENERATION OF THE CEREBRAL CORTEX IN THE COURSE OF PERTUSSIS. FRANK R. FORD, Am. J. Dis. Child. **37**:1046, 1929.

The history of a child, aged 20 months, who developed cerebral diplegia after pertussis is briefly presented. This was found to be due to a great loss of cortical nerve cells unrelated to vascular disturbances or inflammatory processes. This condition was first described by Husler and Spatz and probably represents the anatomic basis of many of the nervous complications of pertussis. The lesions are different from those which have been found in the nervous system following measles and vaccinia.

AUTHOR'S SUMMARY.

CONGENITAL HEMOLYTIC ICTERUS. J. M. MASTERS, LEON G. ZERFAS and HOWARD B. METTEL, Am. J. Dis. Child. **37**:1254, 1929.

Two sisters, aged 5 and 9, with congenital hemolytic icterus were observed for fifteen months before splenectomy without clinical or hematologic evidences of a crisis. Following splenectomy, the red blood cells, hemoglobin content, blood bilirubin and reticulocytes returned to approximately normal levels within a comparatively short time. After splenectomy, the diameter of the red blood cells increased. In the fragility tests, however, the results were unchanged. Eosinophilia was observed in both instances during the postoperative course of the disease.

AUTHORS' SUMMARY.

THE RÔLE OF THE LYMPHATICS IN THE EARLY STAGES OF THE DEVELOPMENT OF OBSTRUCTIVE JAUNDICE. C. MAYO, 2nd, and C. H. GREENE, Am. J. Physiol. **89**:280, 1929.

While in dogs it was found that bilirubin and bile acids accumulate rapidly in the blood stream after ligation of the cystic and common ducts, there was an even

more rapid accumulation in the lymph. Drainage of the lymph by a fistula of the thoracic duct delayed the changes in the blood stream but did not prevent the development of jaundice. Ligation of the thoracic duct had less effect than did the establishment of the fistula. The lymph channels appeared to be the most active agents of bile resorption during the first hours of obstructive jaundice.

H. E. EGGERS.

CONGENITAL PYLORIC OBSTRUCTION (AN EXPERIMENTAL STUDY). J. L. BRODIE, Am. J. Physiol. **89**:340, 1929.

In rats born of mothers fed on a diet with minimal antineuritic vitamin content, ten of twenty-three showed congenital pyloric obstruction. In those cases in which the obstruction was of lesser degree, or cured by atrophine, polyneuritis later developed. The vagus in all cases examined showed myelin degeneration. This pyloric obstruction was much commoner in young rats of the second generation than in those of the first, and seven eights of the cases ocurred in males. Attention is called to the points of similarity to congenital obstruction in man.

H. E. EGGERS.

ABSORPTION AND EXCRETION OF ARSENIC, BISMUTH AND MERCURY BY THE COLON. A. J. BARGEN, A. E. OSTERBERG and F. C. MANN, Am. J. Physiol. **89**:640, 1929.

By the use of an ingenious isolated colonic pocket, the absorption and elimination of arsenic, bismuth and mercury by that organ were studied in the dog. It was found that arsenic in the form of neoarsphenamine was readily absorbed from the colon; there was no evidence of absorption of this compound or of a product similar to acetarsone here. Bismuth in the form of sodium tetra-bismuth-tartrate was both absorbed and excreted. Mercury as mercurochrome was not absorbed; nor was it excreted when administered as mercurochrome or diacetoxymercuri-4-nitro-2-cresol, at least for four hours after its intravenous injection. The colonic lesions following the intravenous injection of mercurials the writers believe can be best explained by local irritation, since there is definite evidence of the elimination of these drugs elsewhere in the gastro-intestinal tract.

H. E. EGGERS.

THE METABOLISM IN CHRONIC ARTHRITIS. L. T. SWAIM, J. A. M. A. **93**:259, 1929.

It appears that in arthritis the metabolic rate is reduced, especially in the early stages. A low rate may be a pre-arthritic sign.

INHERITABLE ANHIDROSIS AND ANADONTIA. ELMER ROBERTS, J. A. M. A. **93**:277, 1929.

The pedigree is given of six generations of a family illustrating this abnormality which appears to be sex-linked.

HYPERPARATHYROIDISM. JULIAN D. BOYD, J. E. MILGRAM and G. STEARNS, J. A. M. A. **93**:684, 1929.

Clinical hyperparathyroidism may give rise to functional impairment of the gastro-intestinal, renal, osseous and muscular systems. It causes excessive elimination of calcium salts in the urine, with increase of the serum calcium concentration. The bone salts are mobilized, and varied types of bone dystrophy may result; while most instances have been representative of osteitis fibrosa generalisata, some lesions have been histologically indistinguishable from giant cell tumors. The characteristics of the urine may simulate those of renal insufficiency. The clinical and laboratory data have led to exploration of the parathyroids in four instances, and in each the removal of a parathyroid adenoma has resulted in relief of symptoms.

AUTHORS' SUMMARY.

THE PROGESS OF PHYSIOLOGY. AUGUST KROGH, Science **70**:200, 1929.

"I think the time has come when special chairs and laboratories should be established for the physiology of disease, morbid physiology or experimental medicine. The main point is that the leaders of such laboratories should have no regular duties connected with the treatment of patients, but they must have a small number of beds at their disposal for the temporary study of selected cases, and they must, of course, be in close and constant contact with the clinical wards. They must have facilities for studying disease experimentally on animals. Within the field of blood circulation and innervation of blood vessels with which I am personally acquainted, I have had the desirability and even necessity of cooperation with the practical medicine brought home to me again and again. I have learned also that the theoretical problems regarding kidney function require for their solution a close study of clinical cases, and I cannot doubt for a moment that great benefit to patients will ultimately result from such a study. Much can be done in this direction by means of existing facilities, but I anticipate an acceleration of progress from the creation of special chairs as outlined, and I feel sure that the resulting contributions to practical medicine would amply and within a short space of time repay the communities for the initial outlay on such departments and for their maintenance."

THE SUPRARENAL MEDULLA. L. ELANT, Arch. internat. de méd. expér. 5:69, 1929.

The histophysiology and microscopic changes of the suprarenal medulla were studied in mice, rabbits and dogs. The secretory activity of the gland presents a chromaffin reaction which can be changed in intensity by the injection of certain drugs. This change is brought about by influencing the gland's content of pro-epinephrine, which, in turn, is dependent on a certain equilibrium between assimilation and excretion of epinephrine.

A change in the chromaffin reaction is accompanied by certain histologic manifestations as well as changes in the character of the glandular excretion. Following the injection of strychnine the following picture is presented: preservation of the caliber of the large vessels with dilatation of the capillaries, distention of the intercellular and intracordial spaces, formation of vacuoles at the excretory pole, distinct bipolarity of the medullary cells, enlargement of the vascular zone, marked increase in the size of nuclei, nuclear budding and enlargement of the functioning zone. With diminution in the function of the gland there is decrease in cellular and nuclear volume, effacement of cellular bipolarity, narrowing of the excretory channels and regression of the activity zone. There are also certain changes in intracellular structure.

The effects of injecting insulin, as well as the influence of certain infections, wounds and other pathologic processes, are described and discussed.

PEARL M. ZEEK.

INFLUENCE OF SODIUM PHOSPHATE AND CALCIUM SALTS ON THE EFFICIENCY OF THYROID SUBSTANCES. I. ABELIN, Biochem. Ztschr. **199**:72, 1928.

A ductless gland produces more or less of its specific internal secretion. Besides this central regulation there is also a peripheral regulation which is not less important, since it changes the efficiency and not the amount of the internal secretion. Of many other factors in this peripheral regulation, the different foodstuffs play an important rôle. For instance, it is a well known fact that the efficiency of thyroxin is changed by feeding meat or fat.

The influence of inorganic salts, especially of calcium and phosphates, was studied on rats with hyperthyroidism experimentally produced. The administration of phosphates increased the efficiency of the thyroid substances, while that of calcium salts diminished it. A formation of glycogen in the liver can often be observed after doses of potassium carbonate, in spite of feeding thyroid gland. The calcium

salts seem to have a specific influence on thyroxin only, and do not change the efficiency of epinephrine.

An antagonism between thyroid function and excess of calcium is demonstrated and plays perhaps a rôle in the etiology of goiter.

C. A. HELLWIG.

STUDIES IN IODINE CONTENT OF NORMAL AND PATHOLOGIC THYROID GLANDS. G. LUNDE, K. CLOSS and K. WUELFERT, Biochem. Ztschr. **206**:248, 1929.

Following the method of von Fellenberg, the iodine content of many normal and diseased thyroid glands was determined. Normal Norwegian glands have an average weight of 24.66 Gm. and a total iodine content of 9.86 mg. The relative iodine content of these normal thyroids is 43 mg. per hundred grams of fresh, and 155.29 mg. of dried gland. The iodine content of nodular goiters without hyperthyroidism varies greatly, but is usually much higher than it is generally believed. In the nodular colloid goiter with hyperthyroidism the iodine content was found to be high: from 14.6 to 122.9 mg. per hundred grams of the fresh gland.

The thyroid gland in exophthalmic goiter is poor in iodine and colloid, but it retains both after administration of a compound solution of iodine.

C. A. HELLWIG.

Pathologic Anatomy

PULMONARY ATELECTASIS. HENRY K. MOHLER, Am. J. M. Sc. **177**:507, 1929.

Pulmonary atelectasis not associated with surgical or traumatic conditions occurs more frequently than is generally recognized. Two such cases are reported. The most probable etiology is a mechanical obstruction to the bronchi. The condition has been produced experimentally by injecting into the bronchi of animals material removed from the bronchi of patients suffering from pulmonary atelectasis.

PEARL M. ZEEK.

THE ARTIFICIAL PRODUCTION OF PUNCTATE BASOPHILIA AND RETICULATION IN ERYTHROCYTES. W. E. COOKE, Am. J. M. Sc. **177**:537, 1929.

Punctate basophilia, diffuse polychromasia and reticulation may be produced in any erythrocyte by treatment with benzidine in alcohol and hydrogen peroxide. The stainable substance thus formed is not nuclear in character, but is probably a hemoglobin compound. Its presence may indicate increased permeability or a defect in the lipoid envelop of the erythrocyte. There probably is a close relationship between punctate basophilia, diffuse polychromasia and reticulation and immaturity.

PEARL M. ZEEK.

CHANGES IN THE EYE IN LEUKEMIA. EGBERT J. BORGESON and HENRY P. WAGENER, Am. J. M. Sc. **177**:663, 1929.

The most common retinal picture in all types of leukemia is that of engorged veins associated with hemorrhagic areas and with exudates of deep nodular or superficial cotton-wool type. An irregularly rounded hemorrhagic area with a nodular white center occurring without other retinal lesions usually justifies the diagnosis of acute leukemia. Anemia is an important factor in the causation of retinal lesions in the leukemias. In myelogenous leukemia hemorrhage in the retina is more common than in the skin, subcutaneous tissues and mucous membranes. In lymphatic leukemia the reverse is true.

PEARL M. ZEEK.

CHRONIC BRONCHIECTASIS. EDWARD S. THORPE, JR., Am. J. M. Sc. **177**:759, 1929.

The early pathologic changes seen in this condition are slight interstitial and peribronchial fibrosis at the bases with diaphragmatic pleurisy. The bronchi may show slight annular dilatation, infiltration of the mucosa with loss or distortion of glands, and residual secretion of a tenacious, yellowish-green, mucopurulent character. Bronchopneumonia, pertussis and measles are frequent factors in the etiology since they carry infection deep into the framework of the lungs. Disease of the accessory sinuses helps maintain a state of sepsis. It is of urgent therapeutic value, especially in children, to correlate the early pathologic and clinical observations.

PEARL M. ZEEK.

BILATERAL ANEURYSMS OF THE COMMON ILIAC ARTERIES. HENRY JOACHIM and MAX A. GOLDZIEHER, Am. J. M. Sc. **177**:849, 1929.

A case is presented of a bilateral aneurysm of the common iliac arteries of arteriosclerotic origin in which syphilis was definitely excluded. The diagnosis was arrived at by palpation of a large pulsating mass in the left lower abdominal quadrant, which increased in size during the period of observation. There are only two similar cases reported in the literature.

AUTHORS' SUMMARY.

PERIARTERITIS NODOSA. G. A. BENNETT and S. A. LEVINE, Am. J. M. Sc. **177**: 853, 1929.

A typical case is presented of periarteritis nodosa in a man, aged 22, in whom the disease was associated with hypertension and cardiac and renal insufficiency. At autopsy, nodosities were found along the medium sized arteries.

A second case is presented in which the disease was associated with meningitis of an aseptic type. At autopsy almost all of the blood vessels of the body showed typical nodosities.

PEARL M. ZEEK.

THE SIZE OF THE CONSOLIDATED LUNG IN LOBAR PNEUMONIA. P. N. CORYLLOS and GEORGE L. BIRNBAUM, Am. J. M. Sc. **178**:15, 1929.

The size of the affected lobes in lobar pneumonia, contrary to the generally accepted opinion, is smaller than that of the healthy lobes. The enlargement of the consolidated lung is only apparent and is due to the collapse of the healthy lung when the thoracic cavity is opened. In order to appreciate the true sizes of the consolidated and healthy lobes it is necessary to clamp the trachea and then to open the chest with only the minimum manipulation of the healthy lobes. The decreased size of the pneumonic lobe, as shown by roentgen and postmortem studies, points to a similar pathogenesis in pneumonia and atelectasis. These points definitely proved for the dog need further confirmation for the human being.

AUTHORS' SUMMARY.

CARCINOMATOUS ABSCESS OF THE LUNG. MAURICE FISHBERG and ELI H. RUBIN, Am. J. M. Sc. **178**:20, 1929.

Fifteen cases of primary cancer of the lung are reported in which clinically and at necropsy excavations were found. It appears that in about one third of the cases of neoplastic disease of the lung the neoplasm breaks down, leaving a cavity after the necrotic tissue is eliminated.

It is emphasized that such patients with excavated carcinoma of the lung often present the seemingly typical symptomatology, physical signs and even roentgenoscopic appearance of abscess of the lung. In fact, the simulation of the clinical picture of pulmonary abscess may last for many months. In all instances of apparently primary abscess of the lung of recent onset in elderly persons the possibility of broken-down neoplasm is to be borne in mind.

AUTHORS' SUMMARY.

BRAIN TUMORS IN CHILDHOOD. FREDERIC H. LEAVITT, Am. J. M. Sc. **178**: 229, 1929.

Brain tumors occur with relative frequency in infancy and childhood. The ratio of juvenile to adult cases in this series is 1 to 14, and the favorite location is in the cerebellum, occurring in this situation in more than 60 per cent of the cases. The usual types of tumors encountered are the tuberculomas, the congenital tumors and those of the glioma group. Statistics of recent date, compared to those of twenty years ago, show the lessening frequency of the tuberculous growths. The congenital tumors are generally suprasellar lesions and produce symptoms of dyspituitarism. The glioma group preponderate in childhood regarding both number and malignant state. They are the preadolescent tumor and they constitute about 75 per cent of the new growths in preadolescent brains, and 40 per cent of all brain tumors. In childhood they usually occur in the midcerebellar region, arising from the roof of the fourth ventricle and projecting into the vermis. This situation places them in the most critical position to endanger life and to produce an early internal hydrocephalus by pressure on the iter. The "fetal-rest" theory of the genesis of neoplastic growths is supported by the identical occurrence of cerebellar tumors in monozygotic twins, as reported in this article.

AUTHOR'S SUMMARY.

FIBROSARCOMA OF THE THYROID GLAND. W. O. JOHNSON, Ann. Surg. **40**:29, 1929.

Two cases of fibrosarcoma of the thyroid gland are reported in which the malignant process followed eighteen and twenty-seven years after the appearance of a nodule in the glandular substance.

RICHARD A. LIFVENDAHL.

PRIMARY HYPERNEPHROMA OF THE LIVER. T. L. RAMSEY, Ann. Surg. **40**:41, 1929.

A mass 22 by 15 cm. was removed from the under surface of the right hepatic lobe. The tumor was composed of a connective tissue capsule which was continuous with the liver capsule. The substance had undergone varying degrees of degeneration, and microscopically the cells were similar to those of the adrenal cortex and were arranged in fascicular fashion. The other sites in which adrenal rests are found are reviewed, and the various theories as to the origin of these types of tumors are given.

RICHARD A. LIFVENDAHL.

CUTANEOUS NEUROMA (AN UNUSUAL CASE). W. W. DUEMLING, Arch. Dermat. & Syph. **19**:226, 1929.

The case of an unusual, rapidly forming tumor of the skin resembling an enormous keloid is reported. Histologically, the tumor consisted of bundles of medullated nerve fibers. The tumor is classified as a true neuroma of the skin.

AUTHOR'S SUMMARY.

DERMATOMYOSITIS: A CLINICOPATHOLOGIC STUDY. C. DAVISON, Arch. Dermat. & Syph. **19**:255, 1929.

The clinical progress of a patient with dermatomyositis of two years' duration is reported. There was marked involvement of all the muscles especially of the

sternocleidomastoid, with a sore throat leading to tonsillectomy, followed by pulmonary abscess and finally death. Typical and classic lesions were demonstrated by the autopsy, also a coexisting status lymphaticus.

AUTHOR'S SUMMARY.

GRANULOMA INGUINALE, CULTURE OF THE DONOVAN BODY. M. GAGE, Arch. Dermat. & Syph. **19**:764, 1929.

Bacillus mucosus is a secondary invader of granuloma inguinale. Some believe that it simulates the Donovan bodies. After many unsuccessful attempts, Gage isolated in pure culture an organism from a patient with granuloma inguinale. This organism has all the staining qualities and morphologic characteristics displayed by the Donovan bodies in smears from patients.

FRANK M. COCHEMS.

PURPURA ANNULARIS TELANGIECTODES (MAJOCCHI'S DISEASE). MOSES SCHOLTZ, Arch. Dermat. & Syph. **19**:769, 1929.

The author adds another report to the sixty-three previously recorded instances of Majocchi's disease. In this patient gonorrhea is believed to be the etiologic factor. The lesions are described and differentiated from angioma serpiginosum, Schamberg's disease and poikiloderma vasculare atrophicans. An opinion is advanced that angioma serpiginosum is a progressive nevoid, capillary proliferation of the skin differentiating it from Majocchi's disease, Schamberg's disease and poikiloderma which are inflammatory angiodermatoses.

AUTHOR'S SUMMARY.

LUDWIG'S ANGINA. A. P. C. ASHHURST, Arch. Surg. **18**:2047, 1929.

This is an excellent historical review of this clinical entity, and a discussion of its pathogenesis and treatment. The author points out that the infection in this disease is different from a lymphogenous infection with lymphadenitis in that it is a diffuse, indurative inflammation of the submental tissues not affecting, as a rule, the parotid, submaxillary and sublingual salivary glands. Eighteen cases are presented, in eleven of which the patients gave a definite history indicating that dental infection was the primary source. A discussion of the anatomy of this region, particularly with reference to the fascial planes, shows how the infiltration becomes more or less walled off from invading the glands, but instead infiltrates through the soft tissues and muscles. Experimental injections of dye were used to demonstrate the route by which this infection may spread, and these showed that the dye follows the planes of the fascia and stains some of the muscles. Interestingly enough, this stain did not diffuse appreciably beyond the midline, either in the neck or in the mouth. The mortality is high, and early incision, drainage and treatment are indicated.

N. ENZER.

PERIOSTEAL LYMPHATICS. E. CAMPBELL, Arch. Surg. **18**:2099, 1929.

The lymphatics of the periosteum and long bones were studied in embryo pigs and in a human infant who had died during delivery. The method of study was the injection in the former instances of the lymphatics by way of the thoracic duct. This was not successful. In the case of the infant, india ink was slowly injected into the outer layer of the periosteum under low pressure. The ribs, especially the costochondral junction, were most readily accessible and gave best results. Cats and kittens, dogs and rabbits, and infants similar to the first one studied, were used. By this method a lymph plexus was demonstrated in the periosteum and perichondrium at the costochondral junction in some of the animals. This plexus was largely in the outer layer of the periosteum, but was drained by the larger lymphatic vessels that contained valves. The plexus consisted of many small, thin walled, freely communicating vessels, and no valves could be demonstrated in them. The author was unable to demonstrate penetration of this plexus into the cortex of the bone. However, some penetration was noted at the epiphyseal line.

N. ENZER.

CONGENITAL ATRESIA OF THE BILE DUCTS. L. ROSENBERG and G. E. JUDD, Arch. Surg. **18**:2339, 1929.

A lengthy review is made of the case of an infant aged 3 months, on whom congenital atresia of the bile ducts was demonstrated, and in whom the liver showed a diffuse biliary cirrhosis. A review of the literature is given and a differential diagnosis made. The authors point out particularly that the cirrhosis of the liver is present at birth, and is as much a part of the disease as the atresia of the extrahepatic ducts. The spleen was enlarged in this case, and the authors believe that it was due to hyperplasia of the endothelial system. N. ENZER.

METASTATIC TUMORS OF THE URINARY BLADDER ORIGINATING FROM THE CARCINOMATA OF THE GASTRO-INTESTINAL TRACT. HAROLD B. HERMANN, J. Urol. **22**:257, 1929.

In ten cases of carcinoma of the gastro-intestinal tract in the male, metastasis in the urinary bladder was found but once. In twelve cases of Krukenberg tumors, metastasis was found in the bladder six times. The bladder was involved simultaneously with the tubes and the uterus. The ovaries seem to play a determining rôle in directing metastasis formation to the pelvic organs. In the stage when the ovarian tumor is accompanied by involvement of the pelvic organs, operative treatment is not justified. Bladder symptoms in cases of Krukenberg tumor are due to the carcinomatus infiltration of the bladder. AUTHOR'S SUMMARY.

STUDIES IN THE DYNAMICS OF HISTOGENESIS: XIV. THE REMITTENT BACK-PRESSURE VECTORS OF MUSCLE ACTION IN JOINT RANGE OF MOBILIZATION DETERMINE THE MATURE PATTERN OF HUMAN CANCELLOUS BONE. EBEN J. CAREY, Radiology **13**:127, 1929.

The architecture of mature cancellous bone at mono-axial, biaxial and triaxial joints is determined by the back-pressure vectors of muscle action in joint range of mobilization and not by the static load of body weight.

During development there is a pressure of differential growth that results in so-called "vegetative bone formation" in addition to that of muscle action. The origin of bone is a stiffening process of confined and richly vascularized mesenchymal cells enclosed by a circumscribed membrane, and involves the accelerated proliferation of cells growing centrifugally in a relatively small volume against a limiting extrinsic centripetal resistance. The interaction of the centrifugal and centripetal factors of differential growth creates intra-embryonic environmental pressure. This is known as the allelocatalytic effect or the mutual acceleration of the growth of cells dividing in a relatively small volume by the catalyst of growth. The failure to produce bone by tissue culture in vitro is due to the facts that the pressure of structural organization has been eliminated, and that the so-called "osteoblast" has been regarded as a self-differentiated cell capable of forming bone regardless of environment. Bone produced by differential growth, such as myositis ossificans, usually undergoes atrophy, when energy of repair is equalized, if no functional pressure is brought to bear on the bone.

Selective focal atrophy of cancellous bone groups in the adult dog may be accomplished experimentally by the local surgical excision of the muscle the back-pressure vectors of which resulted in the structural expression of specific groups of cancellous trabeculae.

During the prenatal development of the femur in the fetal cow there is a relative shortening of the femur sixfold in relation to the weight of the thigh muscle from the 32.5 cm. to the 90 cm. stage, as well as a decrease in femoral volume relative to femoral weight. The femoral weight and density increase in direct proportion to the weight of the thigh muscle. The femur is apparently hammered relatively shorter and more consolidated during the prenatal period by growth

resistances, especially the back-pressure of the developing tonic thigh musculature. The mature skeleton is a pressure meter of muscle pull.

The calcar femorale or femoral spur, in the neck of the human femur, is the objective expression of the confluent back-pressure vectors which are the resultants of the actions, primarily, of the extensor gluteus maximus and flexor ileopsoas muscles of the hip in sustaining body weight in the erect posture.

The osteoblast is a dependent cell that acquires its morphologic attributes by the position it occupies in the developing embryo or zone of repair in the adult: it is a reaction cell adequately nourished, and consolidated by the stimulus of compression of structural organization, during the period of differential growth and functional mature maintenance.

EBEN J. CAREY.

INSULIN FAT ATROPHY A TRAUMATIC ATROPHIC PANNICULITIS. H. AVERY, Brit. M. J. **1**:597, 1929.

Fourteen of the twenty-one recorded cases of atrophy of the subcutaneous fat following the injection of insulin occurred in women. The brand of insulin used apparently is no factor in its production but the practice of repeatedly injecting into one region without varying the site evidently leads to its appearance. Dimpling of the skin first appears and is followed by a depression which enlarges in depth and radius and at times involves the muscle. The skin may adhere to the underlying structures, undergoes no gross changes but occasionally has impaired pain, thermal and tactile sensations. Microscopically, infiltrations of lymphocytes and histiocytes have been noted in the region of the cutaneous blood vessels early in the condition and after three years fibrous strands extend from the corium and divide the fat into coarse lobules. Apparently this subcutaneous fat atrophy is not due to the presence of pancreatic lipase in the insulin but is a nonspecific traumatic panniculitis. Injections of insulin, hypertonic dextrose or saline solutions or injections of narcotics by addicts may cause it, and it simulates but is less intense than traumatic fat necrosis of the breast.

GEORGE RUKSTINAT.

THE LYMPHATIC VESSELS OF THE LUNGS AND THE INTRATHORACIC VISCERAL GANGLIA. H. ROUVIÈRE, Ann. d'anat. Path. **6**:113, 1929.

The results of a thorough investigation of the pulmonary lymphatics and of the lymph nodes are given.

B. M. FRIED.

HETEROGENEOUS EPITHELIUM IN THE OVARIES OF CHILDREN. S. AKAGI, Arch. f. Gynäk. **134**:390, 1928.

Numerous ovaries of children were examined and several small cystic epithelial formations consisting of cilated cylindric cells, mucus-producing goblet cells or squamous epithelial cells were observed. Only one type of epithelium was usually present in the individual cysts. In cysts lined by ciliated cells or goblet cells ova were seen. But these cysts are not considered as derivatives of granulosa epithelium, but as results of specific congenital anlagen which were present in the granulosa layer of the ovum. The heterogeneous epithelial cells of the ovary originate from corresponding congenital anlagen of Mueller's epithelium.

W. C. HUEPER.

MELANOTIC PIGMENTATION IN AN OVARIAN CYST. A. LIEPELT, Arch. f. Gynäk. **134**:496, 1928.

Dark brown, granular pigmentations were seen in the basal portions of high cuboidal epithelial cells lining an ovarian cyst the size of a goose egg. Larger masses of this pigment are found in the adjacent connective tissue. It has here an extracellular location. The pseudomucinous cyst is regarded as a part of a dermoid.

W. C. HUEPER.

INHALATION OF DIFFERENT KINDS OF COAL DUST. HAROLD BORCHARDT, Virchows Arch. f. path. Anat. **271**:366, 1929.

Soot, hard coal and soft coal inhaled by rabbits lead to lesions much similar to those in the lungs of man. Soft coal (Braunkohle) stimulates connective tissue formation most. Real pneumonokoniosis was not reproduced.

ALFRED PLAUT.

HISTOLOGY OF GENERALIZED OSTEOPHYTOSIS (OSTEOARTROPATHIE HYPERTROPHIANTE PNEUMIQUE). CURTIS CRUMP, Virchows Arch. f. path. Anat. **271**:467, 1929.

The histology of this disease has never been accurately described. Therefore, 122 sections were taken from the bones of a woman who died with the fully developed picture of Bamberger-Marie's disease caused by an unusually large metastatic carcinoma in the lung. The material included all the bones of the right foot, the fibula, a fragment of the tibia and the ulna. A cambium layer of the periosteum was found practically everywhere although widely varying in thickness. There was no osteophyt without cambium under it; generally the cambium extended much wider than the osteophyt. Osteoblastic layers, however, were often absent. Numerous lymphocytes and a few eosinophil cells were found in the periosteum and sometimes in the adjacent muscle tissue. There were many Sharpey's fibers in the osteophyt. This primary osteophyt consists of fibrous bone, the arrangement of which is mainly caused by the blood vessels and not at all by mechanical functional causes. It may become lamellous bone later, through a process of reconstruction after resorption (Umbau). But in the case described there was no real secondary osteophyt. The deeper layers of the osteophyt and the upper layers of the compact bone become highly porous. The thin trabeculae in this spongy bone are not mere remnants of the original bone substance but rather newly formed thin trabeculae, while the bone itself has been absorbed. The osteophyt may be separated from the bone by a cleft, which is even demonstrable on the x-ray film. The insertions of tendons and muscles are all on this outer tube of osteophyt which more or less completely surrounds the bone. At the points of insertions the osteophyt has been found to be thicker or thinner than in other parts of bone; occasionally it was absent. The cleft later on may be filled by bone. Osteophytic layers of different age can be seen on top of each other. The extreme porosis transforms the compact bone into something similar to a skull bone with thin tabula interna and externa; the thin compacta of the tubular bones of the foot was found completely porotic. During these processes the fatty marrow partly becomes cellular and vascular. Subcortical zones of red marrow are visible on the cut surfaces of the bones. The synovialis contains lymphocytes and some eosinophil cells. In the cartilage some fibrinoid degeneration is found; layers near the joint become clear and show their fibers. A pannus from the periosteum destroys parts of the cartilage, and some destruction is wrought by the bone marrow. Together with the exostoses this gives a picture of arthritis deformans. It is doubtful how far this (toxic?) arthritis is part of the disease in question. Occasionally new cartilage is formed. Under one nail a thin osteophytic layer was found; there was no thickening of the soft parts of the toe tip. It is not certain if this was a true drum stick formation. The histologic examination of the bones and of the other organs, including the glands with internal secretion, revealed nothing about the cause of the disease.

ALFRED PLAUT.

THE HISTOLOGY OF GLANDS OF INTERNAL SECRETION IN CHONDRODYSTROPHIC CHICK EMBRYOS. WALTER LANDAUER, Virchows Arch. f. path. Anat. **271**: 534, 1929.

Thymus thyroid parathyroids and epiphysis of chondrodystrophic chick embryos are retarded in their development and offer no explanation for the disease. In the

anterior lobe of hypophysis the arrangement of follicles is disturbed and the whole organ is much smaller. Perhaps the smallness of the sella turcica is responsible for that.

ALFRED PLAUT.

MORPHOLOGY AND FUNCTION OF THE LYMPHATIC TISSUE. J. WAETJEN, Virchows Arch. f. path. Anat. **271**:556, 1929.

Discussion of the function of the germinal centers is given. They are not the only point at which lymphocytes are formed; on the other hand, it is impossible to deny that lymphocytes are formed in them. If the germinal centers are the seat of normal destruction of lymphocytes, why then are they so numerous and persistent in the tonsils? The formation of germinal centers indicates the presence of a cell-damaging agent. The fact that radiation attacks the germinal centers so easily is consistent with the conception that it is the seat of cell formation. In the question of function of lymph nodes it is especially difficult to draw conclusions from the morphologic pictures.

ALFRED PLAUT.

PROGRESSIVE MULTICENTRIC CYSTIC-PAPILLARY ADENOMATOSIS OF PANCREAS. ROSARIO MARZIANI, Virchows Arch. f. path. Anat. **271**:625, 1929.

The author reports the case of a woman, aged 68. The condition was found accidentally at autopsy. The pancreas, which was normal in length, was partly thickened. On the caput a thin-walled cyst the size of a pigeon's egg and a few smaller cysts were found. The ducts were intact and there was no inflammation or malformation. The etiology was unknown.

ALFRED PLAUT.

DEPOSITS OF LIPOIDS AND OF IRON IN THE SUPRARENAL GLANDS AND TESTICLES OF BOYS. CARL BLUMENSAAT, Virchows Arch. f. path. Anat. **271**:639, 1929.

This study is based on fifty-one autopsies on boys between 1 and 15 years of age. Twelve had died of tuberculosis, eight of diphtheria, six of purulent meningitis, five of pneumonia and five of tumors.

The lipoids in the suprarenal glands decrease during disease just as they do in adults. The lipoids of the germ cells are increased in meningitis only. In the interstitial cells a slight increase was noted in other infectious diseases also.

Up to the age of 5 years lipoids are nearly absent in the germ cells; they slowly increase up to the beginning of puberty. Iron deposits in both organs were unimportant.

ALFRED PLAUT.

Pathologic Chemistry and Physics

PIGMENT FORMATION. BRUNO BLOCK, Am. J. M. Sc. **177**:609, 1929.

A specific reaction for melanin-forming cells is described. The agent within the cells which is responsible for this reaction has the characteristics of an oxidizing ferment and is probably identical with the natural pigment producing oxydase of the cells. The distribution, localization, characteristics and composition of melanin are discussed.

PEARL M. ZEEK.

CALCIUM AND MAGNESIUM RELATIONS IN THE ANIMAL. W. P. ELMSLIE and H. STEENBOCK, J. Biol. Chem. **82**:611, 1929.

The antagonism manifested between the ions of calcium and magnesium does not appear to be sufficiently pronounced to suggest that the normal calcium balance may be seriously endangered following the ordinary therapeutic administration of a magnesium salt. The addition of an excess of magnesium to the ration of the rat appears to produce no demonstrable effect on the calcium absorption. It does not increase the severity of an already present, rachitic condition. The

selective absorption capacity of the digestive tract apparently represents an adequate protective mechanism for the exclusion of excesses of magnesium.

ARTHUR LOCKE.

ON THE QUESTION OF THE ORIGIN OF URINARY AMMONIA. S. R. BENEDICT and T. P. NASH, JR., J. Biol. Chem. **82**:673, 1929.

Argument is presented for the conception that urinary ammonia is produced within the kidney from urea. Ammonia is regarded as playing no part in the neutralization of acids within the organism, either intracellularly or in the blood stream.

ARTHUR LOCKE.

Microbiology and Parasitology

THE DEMONSTRATION OF TUBERCLE BACILLI IN SMALL CHILDREN WITH PULMONARY TUBERCULOSIS. V. POULSEN, K. A. JENSEN and E. HUSTED, Am. J. Dis. Child. **37**:900, 1929.

It is difficult to demonstrate the presence of tubercle bacilli in pulmonary tuberculosis in children who are so young that they swallow the expectoration. In view of this fact, Poulsen, Jensen and Husted adopted the following method. In the morning after the child has fasted for about six hours the stomach is washed with from 200 to 300 cc. of sterile water. The wash water is then centrifugated. The sediment is homogeneized and stained after Ziehl-Neelsen's method and examined. Cultures are made of the sediment on Petroff's medium and guinea-pigs are also inoculated. A series of fifteen cases was studied, and the microscopic examination showed tubercle bacilli in the majority of cases. In those cases in which the microscopic examination was not positive and in which there were clinical evidences of tuberculosis, the culture and guinea-pig inoculation bore out the diagnosis.

HARRY E. LANDT.

SUMMARY OF INVESTIGATIONS ON THE ETIOLOGY OF TROPICAL SPRUE IN PORTO RICO. C. WEISS, F. LANDRON, O. COSTA-MANDRY and D. WILKES-WEISS, Ann. Int. Med. **2**:1198, 1929.

In a study of eighty-five cases of tropical sprue, the authors found that *Monilia psilosis ashfordi* was present in the feces of the majority of the patients. This fungus could not be recovered from many typical cases, and it was frequently found in the feces of persons not suffering from sprue. Inoculation of human volunteers with scrapings from the tongues of patients with sprue and with cultures of *Monilia psilosis* has given entirely negative results. Attempts to transmit the disease to monkeys by similar inoculations and by feeding the feces of patients with sprue have been equally unsuccessful. Skin tests on patients with sprue and controls with exotoxins and endotoxins of *Monilia psilosis* fail to show an immunologic relationship. The blood of patients with sprue exhibits no monilicidal activity.

The rarity of achlorhydria in sprue is an important point in differentiating the disease from pernicious anemia.

WALTER M. SIMPSON.

TULAREMIA RESEMBLING SPOROTRICHOSIS. B. SHELMIRE, Arch. Dermat. & Syph. **19**:918, 1929.

A patient with tularemia had a cutaneous eruption closely simulating sporotrichosis which could not be excluded on clinical grounds alone. A diagnosis of tularemia was made because of the positive agglutination tests of the patient's blood serum for tularemia, repeated negative cultures for the sporothrix, and the failure of the eruption to respond to potassium iodide by mouth. A clinical feature not in accord with the diagnosis was the subsequent necrosis of the axillary and epitrochlear lymph glands.

AUTHOR'S SUMMARY.

MELITENSIS AND ABORTUS INFECTIONS IN THE UNITED STATES. CHARLES W. WAINWRIGHT, Bull. Johns Hopkins Hosp. **45**:133, 1929.

In America, melitensis infection is confined to the goat raising areas, while abortus infection is general and widespread. The disease presumably abortus infection is much more prevalent than the literature would lead one to suspect. Both infections occur in persons of all age periods, but the occurrence of positive agglutinations in infants suggests the possibility that the disease is more common at this age than is supposed. The majority of cases of both types of infection occur in males. Occupation played an important part in the recorded cases of melitensis infection. The incidence of contact infection from handling goats was so high that the disease assumed, in this small series, the proportions of an occupational disease. The high incidence of laboratory infection with the abortus variety entitles this organism, as well as the melitensis variety, to respect on the part of investigators. Fever was by far the most constant symptom of onset. The severity of the symptoms of onset was certainly greater in the cases of melitensis infection. The striking difference in the occurrence of pain in the back of the neck is worthy of note. The results of physical examination were strikingly negative in both series, and little difference could be seen in the objective observations. Constipation was outstanding in the melitensis group, and there was frequently an associated tympanites. Joint pains and swellings of the joints were much more prominent in the cases of melitensis infection, as was the occurrence of orchitis. The occurrence of the abortus variety in an ovarian cyst six years after initial symptoms demonstrates the possibility of latent foci. Records of absence of relapse were found only for the abortus group. Normal or reduced white cell counts predominated in the series. There was a relative mononucleosis in a large percentage of the cases, but no striking variation could be found in the response in either group. The existence of a proagglutinoid zone makes it imperative that all dilutions be made when the agglutination reaction is sought for, else the possibility of having missed the reaction in low dilution will always be present. There is a possibility of the infection existing in the absence of the agglutination reaction in the serum. The organism may be recovered from the blood and urine without agglutinins being demonstrable in the serum. The temperature curve is much more typical in the melitensis infection, although varied temperature curves occur. The comparison of the two infections shows the melitensis infection to be generally more in accord with that described as malta or undulant fever, and this infection is usually more severe than the abortus infection.

AUTHOR'S SUMMARY.

HEMOLYTIC STREPTOCOCCUS GANGRENE. FRANK L. MELENEY, J. A. M. A. **92**:2009, 1929.

The disease is a clinical entity that should be readily recognized. The most important clinical characteristics are the rapidity of development; the profound prostration of the patient, and the pathognomonic sign, which is a dusky hue of the skin with or without blisters or bullae and usually appearing on the third, fourth or fifth day. It reminds one of erysipelas, but one recognizes at once that it is not erysipelas. Certain clinical and pathologic characteristics distinguish it from the latter disease. The margin is not raised and usually is not clearly defined. Dark blisters and bullae and dusky skin appear early. The condition differs from ordinary streptococcus cellulitis by the greater rapidity of development, by the rarity of lymphangitis and lymphadenitis and by the early appearance of dusky skin or blisters. In sharp contradistinction to other streptococcus infections, incisions should be made as soon as the condition is diagnosed; for the process will promptly subside if the incisions are adequate and the skin, which is not yet dead, will be preserved. Prompt operation makes all the difference between rapid resolution of the process, on the one hand, and great destruction of tissue, if not metastasis and death, on the other.

AUTHOR'S SUMMARY.

THE FILTRABLE ELEMENTS OF THE TUBERCLE BACILLUS. A. CALMETTE, J. VALTIS and A. SAENZ, J. A. M. A. **92**:2086, 1929.

The authors insist on the existence of filtrable elements derived from the tubercle bacillus. They believe that these elements are invisible.

LIVING MENINGOCOCCI IN SPINAL FLUID TWENTY-SIX HOURS AFTER EMBALMMENT. HUNTINGTON WILLIAMS, R. VAN WOERT and V. W. BERGSTROM, J. A. M. A. **93**:437, 1929.

Live meningococci were isolated from the spinal fluid taken post mortem from an 8 year old child.

The child had died on the fourth day of illness. The body had been embalmed (by the cavity method) for twenty-six hours when the spinal puncture was made.

Thirty hours had elapsed from the time of death until the spinal fluid was examined in the laboratory.

The meningococci did not belong to any particular type, but agglutinated polyvalent antimeningococcus immune serum.

Postmortem spinal puncture has been shown to be of value in differential diagnosis, even after embalmment has been completed.

AUTHORS' SUMMARY.

ACUTE ASCENDING MYELITIS DUE TO THE VIRUS OF RABIES. RALPH E. KNUTTI, J. A. M. A. **93**:754, 1929.

The case reported is that of an ascending paralysis due to an acute destructive rabic myelitis. The diagnosis is based on the presence of Negri bodies in ganglion cells of the spinal cord, and on the development of rabies in inoculated rabbits. The case reported is believed to be unique in its pathologic anatomy. An attempt should be made to establish the etiologic agent of every case of a similar nature not only by bacteriologic studies but, in those terminating fatally, by inoculation of rabbits and monkeys with spinal cord to establish the presence of rabic, poliomyelitic or other viruses.

AUTHOR'S SUMMARY.

RICKETTSIA-LIKE ORGANISMS IN THE SCROTAL SAC OF GUINEA-PIGS WITH EUROPEAN TYPHUS. HENRY PINKERTON, J. Infect. Dis. **44**:337, 1929.

Guinea-pigs, inoculated intraperitoneally with European typhus, occasionally show a scrotal reaction similar to that seen in Mexican typhus, but much less conspicuous, more transient and rarely demonstrable during life. They almost invariably, at the end of the incubation period, show a gelatinous exudate on the surface of both visceral and parietal layers of the tunica vaginalis.

Rickettsia-like organisms similar to those described by Mooser in Mexican typhus, and probably identical with them, may be found in smears of this exudate. Morphologically and in their staining reactions, these organisms are indistinguishable from those found in smears from the gut of the European typhus louse. These organisms have been absent from control preparations, and have not multiplied in artificial mediums. In European typhus, an organized exudate, free from demonstrable organisms, is frequently found on the surface of the testes on from the third to the fifth days of fever. Previous infection with Mexican typhus protects a guinea-pig against infection with European typhus, and no organisms can be found in smears from the scrotal sac of these guinea-pigs. Guinea-pigs after recovering from European typhus are likewise immune to Mexican typhus. The reaction in the scrotal sac is regarded, in both strains, as the result of a local preliminary multiplication of the virus. In Mexican typhus, this local reaction is much more severe. Otherwise, the two strains show an essential similarity in the guinea-pig, both clinically and pathologically. The organism described in each

strain is in all probability the cause of the disease with which it is associated, and Mexican and European typhus are probably only slightly different strains of the same disease.

AUTHOR'S SUMMARY.

THE VIABILITY OF THE ORGANISM OF ROCKY MOUNTAIN SPOTTED FEVER IN GLYCEROL. ARTHUR G. KING, J. Infect. Dis. **44**:357, 1929.

The experiments of Spencer and Parker showing the viability of the organism of Rocky Mountain spotted fever in glycerol are in part confirmed. This viability is exceedingly variable, however, existing in 100 per cent of cases up to twenty days, and in only 14 per cent of cases in the period from forty to sixty days. There is no outstanding difference between the effect of 100 per cent glycerol and that of 50 per cent glycerol. Complete dehydration does not seem to be essential.

Brain is distinctly the tissue of choice. There is presented a successful means of maintaining the organism of Rocky Mountain spotted fever in the laboratory by inoculating guinea-pigs successively at four week intervals with the brain of the previous guinea-pig stored in glycerol in the cold room.

AUTHOR'S SUMMARY.

ACTIVITY OF HERPETIC VIRUS IN MICE. H. B. ANDERVONT, J. Infect. Dis. **44**: 383, 1929.

It is believed that a sufficient number of experiments have been performed to justify the conclusion that, with the technic described, mice react to intracranial inoculation of strong herpetic virus with typical encephalitic symptoms. The possibility that other etiologic agents as described by Lauda and Hamm and Cowdry and Nicholson were responsible for the observed symptoms was eliminated by rabbit tests for the herpetic virus. Studies on the response to other routes of infection have not been completed because it was deemed advisable to do such tests when comparing the susceptibility of mice to a weaker strain of virus. These experiments are now in progress. Forty mouse-brain passages of the JB virus over a period of ten months failed to modify its pathogenicity for the rabbit when tested in the brain, cornea or skin. A series of six intracutaneous inoculations in mice gave rise to a fatal encephalitis and had no apparent attenuating influence on the neurotrophic properties of the strain as determined by the rabbit brain and cornea. These results when compared with those of Flexner, who worked with the same virus, imply that the mouse is more susceptible than the guinea-pig.

The observation that young (14 day old) mice are more sensitive to intracutaneous inoculation of the virus might be offered as a reason for the varying results of other investigators, as noted in the beginning of this paper. This observation is also in harmony with results obtained in ascertaining the susceptibility of young and full-grown chickens to the vaccine virus. The work also suggests the feasibility of utilizing mice as a means of propagating herpetic virus for experimental purposes. It does not, however, as yet justify the employment of the mouse as a regular test animal, since with weaker strains the results might be less consistent.

AUTHOR'S SUMMARY.

ALCALIGENES ORGANISM FROM BLOOD OF THREE PATIENTS WITH GANGRENOUS APPENDICITIS. EMIL WEISS, J. Infect. Dis. **44**:394, 1929.

An organism apparently belonging to the genus *Alcaligenes* was isolated in three instances from blood of patients with gangrenous appendicitis. The name *Alcaligenes appendicalis* is suggested for it.

AUTHOR'S SUMMARY.

THE HEAT RESISTANCE OF BACTERIAL SPORES. O. B. WILLIAMS, J. Infect. Dis. **44**:421, 1929.

Evidence gleaned from the literature and accumulated during the progress of this work supports the idea that the cause of death in cells exposed to a high

temperature is the coagulation of bacterial protein. Conditions which render protein more difficult to coagulate consequently result in an increased resistance to heat. The water and the ash content of the cell appear to be especially important in this connection. However, cultivation under certain nutritive conditions which do not appear to be intimately related to either the water or the ash of the cell has invariably resulted in the production of resistant spores.

AUTHOR'S SUMMARY.

VIRULENCE OF B. PARATYPHOSUS B IN WHITE MICE. R. D. FRIEDLANDER and K. F. MEYER, J. Infect. Dis. **44**:466, 1929.

It was found impossible to raise the virulence of a strain *B. aertrycke* for white mice after prolonged passage in the device described by Weiner, either by three or six hour intervals in plain hormone broth or by six hour subcultures in broth containing antiserum for the "rough" type of *B. aertrycke*. The fact that the virulence could not be raised for white mice is explained by the supposition that the strain of *B. aertrycke* was already in a state of maximum virulence for these animals. Finally, the term virulence must be indelibly associated with host-environment, susceptibility and immunity as well as with the invasive powers of any particular organism.

AUTHORS' SUMMARY.

VIRULENCE OF B. PARATYPHOSUS B IN GUINEA-PIGS. R. D. FRIEDLANDER and L. D. HERTERT, J. Infect. Dis. **44**:481, 1929.

It was impracticable to increase the virulence of a strain of *B. aertrycke* for guinea-pigs after passage in plain hormone broth at six hour intervals or in rough antiserum broth at six or twenty-four hour intervals.

The inability to raise the virulence of *B. aertrycke* for guinea-pigs is explained by the fact that these animals offer an unfavorable environment for the growth of this organism as evidenced by the absence of antibody response.

AUTHORS' SUMMARY.

SEDIMENTATION RATE OF RED BLOOD CORPUSCLES IN ACUTE AND CHRONIC INFECTIONS. MARGARET E. WYLIE, J. Infect. Dis. **45**:6, 1929.

The method of Zeckwer and Goodell is easily carried out and gives sufficiently accurate results for clinical purposes. The average rate of sedimentation in all the infections studied was definitely below the normal average. The speed of sedimentation of the red cells varied with different infections but it was not possible to make a specific diagnosis by this method.

The phenomenon is not influenced by the age of the patient, nor by the height of the fever per se. It is probable that the rate of sedimentation is determined by the amount of tissue destruction. It is certainly not dependent, in cases of tuberculous infection at least, on the resistance of the patient. The sedimentation rate varies with the general clinical condition, a decrease in the speed of sedimentation indicating improvement.

AUTHOR'S SUMMARY.

THE CYTOLOGY AND MICROCHEMISTRY OF MYCOBACTERIUM TUBERCULOSIS. GEORGES KNAYSI, J. Infect. Dis. **45**:13, 1929.

The young cell of *Mycobacterium tuberculosis* consists of a membrane presenting thickened areas and granular appendages on its internal surface, which surrounds a very dense, deeply staining cytoplasm permeated by a vacuolar system and inclosing dense, round or oval hyperchromatic granules. The membrane and the granules seem to be made up of similar substances staining metachromatically with dilute old methylene blue solutions (methylthionine chloride, U. S. P.) and taking up iodine and the fat dyes to a great extent. This substance is not removed by boiling in water for one hour, nor by 5 per cent sodium hydroxide, 5 per cent

sulphuric acid, glacial acetic acid or chloroform, at the end of the week. In old cells, the membrane increases in thickness and undergoes, together with the granules, gradual degeneration.

The cell divides by drawing back of the protoplasm and the formation of two closing membranes, without constriction of the mother cell at the zone of division. The granules may divide but they do not seem to be associated constantly with cell division.

The present investigations do not substantiate the assumption of a wax or fat sheath around the cell of the tubercle bacilius or of wax or fat granules inside of the cell.

AUTHOR'S SUMMARY.

COMPARATIVE STUDY OF BACILLUS SORDELLII (HALL AND SCOTT) AND CLOSTRIDIUM OEDEMATOIDES (MELENEY, HUMPHREYS AND CARP). IVAN C. HALL, MARION REINHARDT RYMER and ERWIN JUNGHERR, J. Infect. Dis. **45**:42, 1929.

Bacillus sordellii and *Clostridium oedematoides* are identical species in all essential morphologic and cultural properties and in their toxin-antitoxin reactions.

AUTHORS' SUMMARY.

THE OCCURRENCE OF NONTOXIC STRAINS OF CL. PARABOTULINUM. J. B. GUNNISON and K. F. MEYER, J. Infect. Dis. **45**:79, 1929.

Nontoxic strains which are morphologically, culturally and serologically identical with *Clostridium parabotulinum* have been isolated repeatedly from contaminated food products. The toxic and atoxic elements present in a sample may be considered as variants of the same organism. The three nontoxic strains isolated in this laboratory from home canned corn, home canned Bartlett pears and pickled spiced sardines are agglutinated by antiserums of group 5 type B. Nontoxic cultures of anerobes resembling *Cl. parabotulinum* should not be classified as *Cl. sporogenes* until serologic tests have been made.

AUTHORS' SUMMARY.

COMPARATIVE STUDY OF NONTOXIC AND TOXIC STRAINS OF CL. PARABOTULINUM. C. T. TOWNSEND, J. Infect. Dis. **45**:87, 1929.

It is not possible to differentiate toxic from nontoxic strains of *Cl parabotulinum* by the usual cultural, biochemical and serologic methods.

AUTHOR'S SUMMARY.

EUROPEAN STRAINS OF CL. BOTULINUM. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45**:96, 1929.

A comparative study of six purified strains of organisms isolated from several food specimens and one sample of soil obtained from Europe has revealed the following facts:

Clostridium parabotulinum type A strains indistinguishable from the American strains and the Lister strain 95 have been isolated from botulinogenous food products and a soil specimen. A type B strain of *Cl. parabotulinum* has been obtained from Italian commercially canned shalots.

A nonovolytic type B strain of *Cl. botulinum* recovered from a ham in Germany resembles morphologically, culturally and biochemically the original Ellezelles strain described by Van Ermengem and the various other strains studied by Schumacher, Ornstein, Bitter, Semerau and Noack, Bourmer and Doetsch and others. It differs from the Lister strain 94 by its inability to utilize inosite, its lower peptolytic properties, the production of a relatively weak toxin and the serologic ultraspecificity. The thermal death time of the spores of this organism is less than five minutes at 80 C.

AUTHORS' SUMMARY.

SOUTH AFRICAN CULTURES OF CL. BOTULINUM AND PARABOTULINUM. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45**:106, 1929.

A comparative study of eight cultures of anaerobes secured from South Africa has established the following facts. A nonovolytic, nonsarcolytic organism which elaborates a highly potent neurotoxin was found in two cultures. Pharmacologically, this poison acts like the botulinum toxin on small laboratory animals and monkeys. It is not neutralized by any of the known type A, B and C antitoxins. For this bacillus the designation *Clostridium botulinum* type D (Theiler and Robinson) is proposed. Two cultures although nontoxic contained anaerobic bacteria which corresponded morphologically, culturally and biochemically with the descriptions given by Theiler and Robinson for their *Cl. parabotulinum equi*. One culture when received contained a type A toxin. From this culture a moderately proteolytic *Cl. parabotulinum* type A which differs from the American and European strains of this species has been isolated. From a second culture an anaerobe with similar properties was demonstrated. The significance of these observations is discussed.

AUTHORS' SUMMARY.

CULTURAL STUDY OF AN INTERNATIONAL COLLECTION OF CL. BOTULINUM AND PARABOTULINUM. J. B. GUNNISON and K. F. MEYER, J. Infect. Dis. **45**:119, 1929.

Cultural, biochemical and serologic studies conducted with the simplest medium and by the use of the simplest technic with fifty-three strains concerned in human and animal botulism have shown that the action on native protein, the peptolytic property, the fermentation reactions, the agglutination and the toxin-antitoxin neutralization test are of importance for classification.

On the basis of cultural and peptolytic behavior the anaerobes are arranged in two groups: *Clostridium botulinum* (nonovolytic, Sörensen figures 1 to 6) and *Cl. parabotulinum* (ovolytic, Sörensen figures 18 to 21).

The agglutination tests subdivide the four, possibly five, toxicologic types (A, B, Cα, Cβ and D) into at least fifteen subgroups while the fermentation reactions place the strains in at least eight groups.

Strains fundamentally different from those commonly encountered on the North American continent have been isolated in Europe, Australia and Africa.

AUTHORS' SUMMARY.

BOTULISM DUE TO HOME CANNED BARTLETT PEARS. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45**:135, 1929.

A mother and a daughter tasted and swallowed portions of sliced home preserved Bartlett pears which had shown definite signs of spoilage and fermentation. Symptoms of botulism developed within from five to six hours and death occurred within thirty and forty-two hours respectively after the fatal meal.

The pears were probably preserved by the open kettle method. They contained *Cl. parabotulinum* type A toxin (guinea-pig MLD, 0.001 cc.). The reaction of the syrup was p_H 3.86. Aside from the toxicogenic anaerobe, a yeast and a representative of the lactobacillus group were isolated in pure culture.

Experimental studies have shown that *Cl. parabotulinum* found in the spoiled pears produces spores which survive from two to three hours boiling. They may germinate and elaborate the deadly poison in cooked Bartlett pears irrespective of the acidity, provided certain bacteria or yeasts are growing concomitantly.

Heated spores of *Cl. parabotulinum* failed to germinate in tubes of sterile pear juice with the p_H adjusted to 6. Although in several instances heated spores germinated and multiplied when inoculated into jars or cans of pears, no toxin was produced.

It is probable that certain fruits and acid vegetables owe their immunity from botulinum spoilage less to their acidity than to the absence of food substances essential to the elaboration of toxin.

AUTHORS' SUMMARY.

THE OCCURRENCE OF BACILLUS SORDELLII IN ICTEROHEMOGLOBINURIA OF CATTLE IN NEVADA. IVAN C. HALL, J. Infect. Dis. **45**:156, 1929.

Two strains of a previously unidentified pathogenic anaerobe isolated in 1919 and 1921 by L. R. Vawter of Reno, Nev., from typical cases of icterohemoglobinuria in cattle and against which he prepared an effective antitoxic serum, have been proved to belong to the species *B. sordellii*. This is the third locality in the world in which *B. sordellii* has been recognized, previous cultures having been isolated in the Argentine and New York.

The Nevada strains of *B. sordelli* are regarded as probably secondary invaders in icterohemoglobinuria, the primary cause of which is believed to be *Bacillus hemolyticus*.

Bacillus hemolyticus resembles *B. sordellii* in its vegetative morphology and gram-staining reaction, its sluggish motility, its fermentation reactions with the exception of maltose and its action on gelatin, and differs from *B. sordellii* in its sparse production of spores by old cultures, its weaker proteolytic action, its failure to ferment maltose, its hemolytic action on blood in culture medium, its marked tendency to produce congestion in animals and in the specific antigenicity of its soluble toxin.

AUTHOR'S SUMMARY.

A METHOD FOR THE STUDY OF BACTERIOPHAGE MULTIPLICATION IN BROTH. F. M. BURNET, Brit. J. Exper. Path. **10**:109, 1929.

A method is described by which the first stages of multiplication of a single phage particle in broth can be followed. The results show that the first increase occurs suddenly. In the two cases described there is a sudden appearance of about ten and of about forty demonstrable particles where one was present initially. The time of first increase after addition of phage may vary widely for different types of phages and for different particles in the same filtrate. Phage increase in broth is due, in the early stages at least, to the liberation at lysis of particles that have multiplied in or on a sensitive bacterium.

AUTHOR'S SUMMARY.

INOCULATION OF TYPHUS FEVER BY THE NASAL AND CONJUNCTIVAL MUCOSAE. HELEN SPARROW and UGO LUMBROSO, Arch. Inst. Pasteur de Tunis **18**:1, 1929.

Charles Nicolle established the fact that typhus fever is transmitted by lice through the act of feeding. Subsequently it was found that the intestinal content of the louse is infectious when applied to the bruised or cut skin. It was moreover noted that an accidental contamination of the conjunctiva with virulent material caused the disease.

The experiments reported by the authors were the inoculations of guinea-pigs by way of the healthy conjunctiva. The virus used was a laboratory strain transmitted from animal to animal by inoculation of cerebral tissue from infected guinea-pigs. The results obtained are to the effect that it is possible at times to infect guinea-pigs by placing the typhus virus on the healthy conjunctiva. Positive results are still more often obtained when the conjunctiva is previously prepared with bile. In animals infected in this manner, the incubation period is long, and the disease is mild and not followed by the development of an immunity. Guinea-pigs infected by way of the nasal mucosa invariably contract the disease. Sparrow and Lumbroso believe that the difference in the results obtained is caused by the fact that the eye represents a small surface absorbing an insignificant amount of material, which is not the case with the mucous membrane of the nose.

B. M. FRIED.

PATHOGENIC POWERS OF B. MELITENSIS AND B. ABORTUS FOR MAN AND FOR MONKEY. E. BURNET and E. CONSEIL, Arch. Inst. Pasteur de Tunis **18**:21, 1929.

Five years ago the authors concluded from experiments on man and on monkeys that *Bacillus abortus* was differentiated from *B. melitensis* by lack of pathogenic

power. Also, it was concluded that *B. abortus* vaccinates man and monkey against *B. melitensis*. The matter has been reinvestigated because of many reports of undulant fever in which there is an association with cows and in which *B. melitensis* is not suspected. The cultures used in the present work were more recently isolated than those used in the old experiments. The results secured on three monkeys and three men were similar. *B. abortus* vaccinates against *B. melitensis* but does not give true undulant fever. There was, however, some reaction. Fifteen days after inoculation two monkeys gave positive blood cultures. The serum gave positive agglutinations in dilutions from 1:200 to 1:500. The three men became allergic as determined by an intradermal test. All gave positive agglutinations. The immunologic results differed from the 1922 results, at which time essentially no immunologic reactions were observed. One monkey inoculated with a strain of "human abortus" gave an abortus reaction on a cynomolgus monkey. Thus the conclusions are less categorical than those in 1923. Vagaries indicate the necessity for further study and suggest the possibility of the adaptations of strains to new environment. Laboratory and epidemiologic correlation must be insisted on.

M. S. MARSHALL.

CHRONIC KALA AZAR IN TUNIS. CHARLES NICOLLE and CHARLES ANDERSON, Arch. Inst. Pasteur de Tunis **18**:63, 1929.

Twelve case reports of kala-azar in Tunis are added to reports of seventy-three previously published cases.

M. S. MARSHALL.

EXANTHEMATOUS FEVER, ITS IDENTITY WITH INFECTIOUS ERYTHEMA OR EXANTHEMATOUS FEVER OF THE MARSEILLES REGION AND THE "FEBBRE ERRUTIVA" IN ITALY. E. CONSEIL, Arch. Inst. Pasteur de Tunis **18**:86, 1929.

In a general article the author gives the history, clinical study, case reports, laboratory researches, etiologic table of observations for from 1902 to 1929 and the differential diagnosis. His final paragraph follows:

"Eruptive fever is clinically and etiologically differentiated. This has been felt and described by all authors who have observed cases of eruptive fever. They have described without hesitation a new disease, which they have observed under different names, in identical fashion. Comparison of patients of several regions show to the observer that the eruptive fever, infectious erythema and "febbre errutiva," is a single specific disease for which should be given the first name under which it was described, that of "fièvre boutonneuse."

M. S. MARSHALL.

ANGINA LEPTOTHRICA. A. JOSEPH, Deutsche med. Wchnschr. **55**:656, 1929.

The organism causing a chronic pharyngitis characterized by stippled, firmly adherent, yellow deposits in the mucosa without systemic disturbance was found in two patients to be *Leptothrix buccalis*.

PAUL J. BRESLICH.

SPIROCHAETA PALLIDA IN THE TISSUES OF INFECTED MICE. F. JAHNEL and R. PRIGGE, Deutsche med. Wchnschr. **55**:694, 1929.

In seven white mice inoculated intraperitoneally with material from primary syphilitic lesions, spirochetes were demonstrated in the lymph nodes of the groin and axilla, and in the popliteal lymph node in one mouse. The infection was symptomless, but in sections of the tissues, spirochetes were found, especially in the kidney but never in the central nervous system. The mice were killed at intervals of from sixty-seven to one hundred and seventy-nine days after inoculation.

PAUL J. BRESLICH.

Immunology

THE SENSITIZATION OF RABBITS TO PRODUCTS OF THE PNEUMOCOCCUS. C. G. BULL and C. M. MCKEE, Am. J. Hyg. **9**:666, 1929.

Rabbits having recovered from an acute infection with pneumococci are hypersensitive to an autolysate of the homologous organism. The hypersensitive state can be demonstrated from forty-eight hours to at least four months after the infection, the height occurring shortly after recovery from infection. Immunized rabbits are also sensitive to the autolysate, but to a less degree. Rabbits having recovered from infection with pneumococci and having been made carriers of *Bacterium lepisepticum* developed infections by the latter organism within a few hours after pneumococcus autolysate was put into the nostrils, probably because of hypersensitive shock of the tissues of the portal of entry. PEARL ZEEK.

AN ENQUIRY CONCERNING THE RÔLE OF ALLERGY, IMMUNITY AND OTHER FACTORS OF IMPORTANCE IN THE PATHOGENESIS OF HUMAN TUBERCULOSIS. ARNOLD RICE RICH and HOWARD A. MCCORDOCK, Bull. Johns Hopkins Hosp. **44**:273, 1929.

The authors present an analysis of the principal factors concerned in the pathogenesis of tuberculosis based on an extensive postmortem experience (200 autopsies on patients ranging in age from 7 weeks to 73 years) and experimental inoculations (1,000 animals) mainly into guinea-pigs and rabbits, carried on during the past several years. "Virulence" is regarded as merely the relative ability of the particular strain of tubercle bacillus under consideration to grow in normal individuals of an animal species that is naturally susceptible to the type from which the strain in question is derived. Resistance is not type specific and infected animals become only relatively immune. Issue is taken with Krause's view on allergy that following infection the body requires an altered reactivity or "altered attitude" toward the bacillus, and it is believed that this altered reactivity is essentially quantitative rather than qualitative. It is not an accurate generalization to say that the reaction to the first contact with the bacillus is always tubercle formation, and that exudative inflammation never occurs except in the allergic animal. Either the normal or the allergic animal can respond with either tubercle formation or exudative inflammation and the type of reaction will depend greatly on the number of bacilli and where they lodge. There is no proof that hypersensitiveness is responsible or necessary for the delayed spread, or for the more prominent death of the bacilli in the infected, resistant body. The mechanical effect of the allergic acute inflammation is not the fundamental mechanism which holds the bacilli of reinfection locally. Although it is at present widely believed that the allergic reaction is an essential mechanism of immunity, there is no proof that this reaction is necessary for the more rapid death of bacilli in the immune body. The essence of the matter of acquired resistance is that the bacilli cannot thrive as well in the previously infected body as in the normal one; although at present unable to speak with certainty of the meaning of allergy in relation to immunity, the authors believe that the bodily change responsible for this acquired interference with the life of the bacillus is, in whatever it consists, separate and distinct from the forces that are concerned in the allergic inflammatory — necrotizing tendency. Any beneficial effect that may follow treatment with tuberculin is less referable to perifocal inflammation than to desensitization, and the "stimulation of fibrosis" by perifocal allergic reactions is unnecessary. Encapsulation of a tuberculous focus by connective tissue is merely a process of nonspecific repair and is not a part of the process of inflammation. The allergic hypersensitive reaction is not specifically an attack on living bacilli but follows, in extreme degree, the injection of a simple water extract of the powdered bacillus. The allergic state in tuberculosis represents an increased capacity on the part of the tissues to react, not against living bacilli, but to a bacterial antigen that is liberated as a result of the disintegration of the bacilli, and the authors believe that the

mechanism leading to the death of the bacilli is in operation before the allergic reaction begins. The inflammation of allergy is protective only in that it helps neutralize the injurious effects of the products of bacterial disintegration in the hypersensitive body. An animal may be highly anaphylactic to tuberculoprotein and yet possess not the slightest degree of acquired immunity, or it may be highly immune to the bacillus, after infection, and yet not at all anaphylactic to tuberculoprotein. Although tuberculoprotein calls forth the allergic inflammatory reaction it never causes the formation of tubercles. The allergic resistant body does not change the bacillus of infection so that when introduced into a normal animal it produces a lesion different in any way from that which it originally produced. Unquestionably, with the proper dose properly placed, either the allergic or the nonallergic body can be made to react with either exudative inflammation or tubercle formation, but the allergic body has a markedly greater tendency to react exudatively than has the nonallergic. Any absolute and dogmatic distinction between the types of lesions developing under these two states of reactivity is unwarranted. The terms "exudative" and "proliferative" are useful for the description of what is seen in any case, but are dangerous if used as catch words, or as synonyms for states of resistance.

Miliary tuberculosis must be regarded as nothing more than the result of a septicemia with the tubercle bacillus. So far as is known, there is no inherent difference between the normal bodies of children and of adults which might account for the observed differences in reaction to the bacillus. The essence of the resistance question seems to lie not in the ability of the body to form connective tissue about the bacilli but in the inability of the bacilli to propagate freely in the particular body in question. In place of Krause's aphorism that "the patient is as resistant as the shell of his tubercle" the authors believe that "the patient is as resistant as his acquired ability to hold in check the growth of tubercle bacilli." The lymphatic anatomy of the lung of human beings at different age periods is of little importance in determining the distribution or character of tuberculous involvement, or the degree to which the regional nodes will be involved. The division of tuberculous infection into three stages comparable to syphilis (according to Ranke) is artificial, unnecessary and unsupported by fact. To say from sections from a case of tuberculosis with certainty just what has happened to the individual is completely out of the question, for the decision is always the result of: (1) the number of bacilli originally deposited at the site, (2) their virulence, (3) the length of time they have been at that particular spot, (4) the character of the tissue in which the bacilli lodge, (5) the degree of resistance (natural, individual and acquired) of the person and (6) the degree of allergy. Even massive blood stream infection in the human being does not produce extensive areas of tuberculous pneumonia. Areas of fresh caseous pneumonia of any extent are not produced in the human being in any other way than by the discharge of bacilli or bacillary products directly into alveoli from older foci in communication with bronchi, for only in this way can large numbers of bacilli reach a large area suddenly. The authors have never failed to find a discharging focus of this sort in their autopsy material when large areas of tuberculous pneumonia were present. Disseminated small foci of pneumonia can result from infection of the lung by way of either the blood stream or the bronchi. The pulmonary lesions of adult life in civilized communities are almost invariably lesions of reinfection, whether exogenous or endogenous in origin, and they begin as a rule, for reasons which are not yet clear, at or near the apex of the lung. The various types of lesions and reactions in the lungs of adults and children are discussed in the light of the authors' conceptions, and these principles are applied to the pathogenesis of the diffuse exudative tuberculous meningitis. The factors of high allergy plus the presence of abundant circulating bacilli are not sufficient in themselves to bring about exudative tuberculous meningitis in rabbits and guinea-pigs, but the direct injection of tubercle bacilli into the subarachnoid space is successful. A careful search for local caseous lesions in communication with the meninges serving as a foci of discharge of bacilli directly into the subarachnoid

space was successful in thirty-eight or forty cases of diffuse tuberculous meningitis; in seven, no generalized miliary tuberculosis existed, but one or more caseous foci existed in the brain. It is clear that disseminated tubercles in the brain are frequent complications of progressive visceral tuberculosis. Infection of the ependyma is not to be regarded as an evidence of blood stream dissemination of bacilli since bacilli can reach the ventricles by retrograde transport from the subarachnoid space. Tuberculous meningitis is not a direct result of septicemia with the tubercle bacillus but depends on the presence of local lesions which discharge bacilli into the subarachnoid space. Blood stream infection can occur as a result of tuberculous meningitis. What is true of the meninges is equally true of serous cavities in general; without question, in each such case a local tuberculous focus must have ruptured into the serous cavity—a caseous subpleural lymph node, a focus at the surface of the lung or a cold abscess in association with vertebral tuberculosis, discharging bacilli into a pleural cavity; a caseous focus in bone or cartilage discharging into a joint; a tuberculous Fallopian tube or caseous mesenteric lymph node discharging into the peritoneal cavity; a tuberculous lymph node involving the pericardium, or a direct extension from pleural tuberculosis.

H. J. CORPER.

STUDIES IN ISOHEMAGGLUTINATION: THEORETICAL CONSIDERATIONS. ALEXANDER S. WIENER, MAX LEDERER and S. H. POLAYES, J. Immunol. **16**:469, 1929.

Of all the theories on the heredity of blood groups that have been presented up to the present time, Bernstein's theory is most satisfactory. Apparent exceptions to this theory are due to: faulty technic; failure to test a sufficient number of people; errors in computation; failure to study a homogeneous group, and selection of a subgroup for study which is not representative of the entire group.

AUTHORS' SUMMARY.

QUANTITATIVE STUDIES ON THE ACTION OF COMPOUND HEMOLYSINS. RUDOLF GAHL, J. Immunol. **16**:483, 1929.

A quantitative study of the characteristic curves defined in preceding papers led to the conclusion that the complexities of these curves as they are experimentally obtained can be removed and the curves so simplified that they assume forms which are in harmony with the views proposed by Svante Arrhenius on the reaction between hemolytic amboceptor and complement by introducing the assumption into the calculation that neither heat inactivated hemolytic amboceptor serum is free from complement nor complement serum from natural amboceptor. Geometrical methods for introducing suitable corrections were developed for this purpose. The application of such methods permits the quantitative estimation of the contaminations. Heat inactivated hemolytic amboceptor serum may, when undiluted, contain complement in quantities not much lower in order of magnitude than the complement serum. Its effect may nevertheless not be noticeable on the Wassermann reaction as long as potent amboceptor serum is used which permits a correspondingly high dilution. Application of the law of chemical mass action makes the construction of theoretical systems of characteristic curves possible. Only the exponents of the mass law equations determine the shape of these curves. Such curve systems were calculated under various assumptions regarding the chemical combination between amboceptor and complement and found to present typical pictures characteristic of each reaction. It was shown that when the corrections referred to are applied to the curves derived from the law of chemical mass action in the opposite direction complex curves result which agree with those experimentally obtained within the limits of experimental errors except in the region of complement deviation which the theory is not designed to cover. Rational systems for expressing strength of amboceptor and complement were proposed. Conclusions were drawn regarding the relative molar concentrations of amboceptor and complement. The assumption of a stoichiometric chemical reaction between amboceptor and comple-

ment explains all observations. The stipulation of an enzymatic nature of one or both does not seem justified. Summing up the results of all four papers on this subject, we might state that while Manwaring rightfully pointed out that Arrhenius' mathematical representation of the reaction between hemolytic amboceptor, complement and red blood cells is not in agreement with the experimental facts, we find it in agreement with them so far as only the reaction between amboceptor and complement is concerned. The constants which Arrhenius used in his equations are as all constants obtained by experiment subject to revision by later investigators.

AUTHOR'S SUMMARY.

THE SKIN REACTION IN THE SENSITIZED GUINEA-PIG. SUSAN GRIFFITH RAMSDELL, J. Immunol. **16**:509, 1929.

Guinea-pigs actively sensitized and skin tested, using trypan blue as a technical aid, gave reactions to the antigen serum in dilutions as high as 1 : 10,000. Passive sensitization of the skin of a normal animal could be demonstrated as early as the sixth day after treatment of the actively sensitized animal, and was regularly more consistent than the test for passive sensitization by shock. Whether the antibody responsible for the skin reaction is a separate one from the anaphylactic antibody or merely an extension of its manifestation is not clear.

AUTHOR'S SUMMARY.

DISTRIBUTION OF ANTIBODIES IN THE SERUM AND ORGANS OF RABBITS. JULES FREUND, J. Immunol. **16**:515, 1929.

When rabbit serum containing precipitin is injected into the dermis of a rabbit, the site of injection reacts to a subsequent injection of egg white with specific inflammation (Arthus phenomenon). The state of sensitiveness is of short duration; it cannot be demonstrated from four to eighteen hours after passive sensitization. When rabbit serum containing agglutinins is injected into the skin of a rabbit, the agglutinins disappear from the skin within from six to twelve days. For the first five days the site of injection contains more agglutinins per gram of tissue than the noninjected parts of the dermis. Later the agglutinins are distributed in the blood and organs as if they had been injected directly into the blood stream. Precipitins and agglutinins differ from atopic reagins in regard to their fixation in the skin.

AUTHOR'S SUMMARY.

THE SCHICK TEST IN PALESTINE, A COUNTRY OF LOW DIPHTHERIA PREVALENCE. A. MANN and I. J. KLIGLER, J. Prev. Med. **3**:309, 1929.

Diphtheria and scarlet fever are relatively far less prevalent in Palestine than in countries having a temperate climate. From about 3,000 Schick tests it appears that the percentage of diphtheria immunes at the ages above 8 in Palestine is the same as found by Zingher in New York City, but that the immunization starts earlier among the Palestine children than in the New York children. A comparison of the native and foreign born groups on the one hand, and the Ashkenazic and Sephardic communities on the other, indicates that the native born, especially in the Sephardic community, develop their diphtheria immunity much earlier than the foreign born children. It would seem, therefore, that the absence of diphtheria in Palestine is only apparent. Since active immunity can probably be acquired only as the result of infection, the infection rate in the early age groups must be relatively high to produce so large a number of immunes.

AUTHORS' SUMMARY.

ANAPHYLACTIC STUDIES WITH EXTRACTS OF HYDATID SCOLICES. C. H. KELLAWAY, Brit. J. Exper. Path. **10**:115, 1929.

Experiments are described which attempt to correlate the characteristics of the hydatid scolex with those of other helminths, the tapeworm (Meyer) and the

fluke (Kellaway). The substances in scolex which are insoluble in acetone but soluble in absolute alcohol and which act as "partial antigens," causing sensitiveness but being unable to discharge it, may possibly owe their activity in vivo to union with some body protein in the guinea-pig producing a foreign complex to which antibody can be produced. There is, however, in addition a water-soluble substance present in saline extracts of scolices which can function as an anaphylactic antigen. Owing to the difficulty of freeing scolices from the protein substances in hydatid fluid, it is not certain that this substance is not derived from hydatid fluid. Finally, host (sheep) serum protein is present in extracts of scolices, and extraction with pure dry acetone and with absolute alcohol does not guarantee its absence from the resulting extracts.

AUTHOR'S SUMMARY.

THE INFLUENCE OF PARENTERALLY GIVEN LIPOIDS ON HEMOLYSIN FORMATION IN RABBITS. HANS GROSS, Centralbl. f. Bakteriol. **109**:8, 1928.

The simultaneous parenteral administration of cholesterol, lecithin and beef heart extract had no influence on the formation of hemolysin subsequent to the injection of sheep's red corpuscles.

PAUL R. CANNON.

THE RELATIONSHIP BETWEEN THE PHAGOCYTOSIS OF ANTIGENIC SUBSTANCES AND ACQUIRED IMMUNITY. S. FUJITSUND, Centralbl. f. Bakteriol. **109**:93, 1928.

The author attempted to correlate the degree of phagocytosis of killed staphylococci following the previous injection of heated and unheated centrifugates of a cholera vibrio vaccine as well as salt solution alone, with the resulting antibody content of the blood. His conclusions are that the antibody content varied directly with the previous phagocytic rate in the same animal.

PAUL R. CANNON.

ENDOCRINE GLANDS AND IMMUNITY. A. SEITZ, Centralbl. f. Bakteriol. **109**:115, 1928.

The phagocytosis of anthrax bacilli in vivo was markedly reduced in the serum of adrenalectomized rats. Simultaneous castration had no further effect. There was also a decrease in the content of bacteriolytic antibodies for the same bacilli. Coincidently, there was a leukopenia of the neutrophils with a lymphocytosis and a thrombopenia. The injection of adrenal extract had no influence on the course of the infection.

PAUL R. CANNON.

THE SIGNIFICANCE OF THE SPLEEN IN SPIROCHETAL INFECTIONS. P. REGENDANZ, Centralbl. f. Bakteriol. **109**:321, 1928.

Regendenz studied the course of infection in opossums artificially infected with *Spirochaeta didelphydis*, especially as to the influence of splenectomy. Only two of nine normal opossums died as a result of the infection, whereas all eight of the splenectomized animals died, within a shorter period than the two normal ones. In opossums with a latent infection, splenectomy was followed by a rapid reproduction of the spirochetes. The author concludes that in this spirochetal infection the spleen plays the most important rôle in the formation of antibodies and the establishment of immunity.

PAUL R. CANNON.

A NEW METHOD FOR THE PRODUCTION OF A POTENT DIAGNOSTIC SERUM AGAINST ANTHRAX BACILLI. RAHEL ROSENBERG and D. ROMANOW, Centralbl. f. Bakteriol. **110**:102, 1929.

The reliable diagnosis of anthrax demands a serum of high titer and specificity. The authors obtained this by the immunization of rabbits with the albumin extract of anthrax bacilli, prepared by the method of Fudjiwara (*Ztschr. f. d. ges. gerichtl. Med.*, 1922, Bd. 1), slightly modified. Serums highly specific and with titers as

high as 1:100,000 were thus obtained. Organ extracts from animals infected with anthrax gave precipitation reactions with these serums. The serums also retained their strength for long periods, but were of no value therapeutically.

PAUL R. CANNON.

THE RÔLE OF THE SKIN IN THE PRODUCTION OF SPECIFIC ANTI-ANTHRAX SERUMS. G. KUDRJAWZEW and D. ROMANOW, Centralbl. f. Bacteriol. **110**:164, 1929.

The intracutaneous injection of a virulent culture of anthrax bacilli into horses over a period of three months led to no formation of specific antibodies that could be detected in the blood. The later intravenous and subcutaneous injection of anthrax organisms into such animals was followed by a more rapid formation of antibodies than in animals not previously injected intracutaneously.

PAUL R. CANNON.

TUBERCULIN ALLERGY AND IMMUNITY IN TUBERCULOSIS. A. CALMETTE, Ztschr. f. Tuberk. **53**:193, 1929.

The traditional opinion that immunity is impossible without allergy is erroneous. It has been shown in various experiments that animals infected with a small amount of tubercle bacilli may lose their allergy after a time and still show a definite resistance against reinfection, and that animals may harbor tubercle bacilli or even healing tuberculous lesions without being allergic. The immunity is dependent only on the presence of living tubercle bacilli regardless of the absence or presence of allergy. This concept is borne out by the experiments with B. C. G. immunization in babies, who frequently do not develop allergy and still are undoubtedly protected from reinfection. Following oral immunization, at least 50 per cent of children develop allergy at some time or other within the first year; following subcutaneous immunization, all children develop allergy.

MAX PINNER.

Tumors

LEUKOSARCOMA. DAVID H. FLASHMAN and SIMON S. LEOPOLD, Am. J. M. Sc. **177**:651, 1929.

A white man, aged 60, had a swelling in the right groin for a year. Biopsy revealed lymphosarcoma. The leukocyte count was normal. He was given treatments with roentgen ray for about five months, during which the blood was still normal. A month later, he developed leukemia, and the count rose to 444,000 cells per cubic millimeter with from 90 to 96 per cent small lymphocytes. At autopsy, the changes were of a character intermediate between lymphosarcoma and lymphatic leukemia, rather than a combination of changes marking two separate entities.

PEARL ZEEK.

TUMORS AND TUMOR-LIKE LESIONS OF THE BREAST IN ASSOCIATION WITH PREGNANCY AND LACTATION. A. R. KILGORE, Arch. Surg. **18**:2079, 1929.

Appended to this article is a discussion by Dr. Bloodgood on the treatment of "lactation tumors" and their diagnosis. Dr. Bloodgood strongly favors the use of frozen sections. Dr. Kilgore analyzed these tumors in an effort to determine their etiology and course. In a review of the literature, it was found that of 1,521 lesions of the breast, not including chronic cystic mastitis and acute inflammatory mastitis, 6.3 per cent were first observed by the patient in connection with pregnancy or lactation. Of these lesions, 83 per cent were cancers, galactoceles, tuberculosis or encapsulated adenomas. Twenty-six per cent of the cases of tuberculosis of the breast were first discovered during pregnancy or lactation. Possibly, this might be attributed to the increased functional activities, causing lighting up of a latent focus. More than 90 per cent of the cancers were in women above the age

of 30, and nearly 70 per cent of the benign tumors were in women under 30. It was found that all varieties of tumor may be observed by the patient at any stage in pregnancy or lactation. Of forty-six lactation cancers, eight were well after from four and a half to twenty-one years. Of seven cases without involvement of the axillary glands, five were cured, and of 26 cases with involvement of the axillary glands, three were cured.

N. ENZER.

RADIO-SENSITIVE INTRA-ORAL TUMORS. MAX CUTLER, Arch. Surg. **18**:2303, 1929.

In the past few years, a group of tumors that occur in the nasopharyngeal and tonsillar region has been recognized from two points of view, namely, their histologic structure and their reaction to radiation. There are two main types: those in which there is an epithelial and lymphoid structure, conveniently called lympho-epitheliomas; and epithelial and transitional cell tumors exhibiting the anaplasia of epidermoid carcinoma. In the former there are syncytial masses of cells like epithelial cells, and the tumor is diffusely infiltrated with lymphocytes. In the latter there is a diffuse epithelial structure and absence of lymphocytes. Lympho-epitheliomas have been described as occurring in the tonsillar region and in the pharynx. Their structure resembles that of endothelioma or reticulum cell lymphosarcoma. The dual histologic picture forms the basis of the term "lympho-epithelioma." These tumors are relatively rare, only 6.3 per cent having been found in 300 tumors of the tongue, tonsils and nasopharynx in Ewing's experience. The transitional cell carcinoma is an undifferentiated, neoplastic, large cell tumor somewhat resembling large cell lymphosarcoma. Early involvement of the regional lymph nodes occurs here. This group comprises about 10 per cent of the epitheliomas of the nasopharynx. The primary lesion of these tumors is small, frequently insignificant and difficult to discover. The tumors often become manifest at first by cervical adenopathy. Visceral metastases are common. The liver and retroperitoneal lymph nodes, bones and vertebrae have been the seats of the metastases of this tumor. Clinically, patients usually present themselves on account of cervical adenopathy, and ulceration and pain and bleeding in the primary tumor may not occur until late. This group of tumors is particularly sensitive to radiation. Rapid regression and disappearance of both the primary lesion and the adenopathy occur in response to relatively weak doses. The tumor recurs rapidly, unless the radiation is continued to the point of sterilization. Nine patients who had this disease are reported to be well and apparently free of it after three years.

N. ENZER.

SKIN PRINTS IN LESIONS OF THE BREAST. J. O. BOWER and J. H. CLARK, Arch. Surg. **18**:2386, 1929.

The authors present several prints of the breast showing the differences in the pores and markings of the skin as between persons and as between lesions of the breast. It is claimed that this method demonstrates clearly differences in the skin not so well demonstrated by other methods. In malignant lesions, there is a tendency toward contraction of the pores of the skin if the tumor is more fibrous, whereas if the tumor is increasing rapidly, there seems to be a marked increase in the size of the pores. Thus far, no definite deductions have been made, yet it would seem that this method might uncover characteristic changes in the epidermis associated with lesions in the breast.

N. ENZER.

TUMOR FORMATION FOLLOWING FREEZING WITH CARBON DIOXIDE SNOW. I. BERENBLUM, Brit. J. Exper. Path. **10**:179, 1929.

Repeated mild freezing of the skin of mice with carbon dioxide snow over a long period may lead to the development of malignant tumors. Only a small percentage of mice respond in this manner, and the time necessary to produce such tumors is much longer than with the use of a carcinogenic tar. When the skin

of mice is subjected to repeated freezing and tarring, warts appear at the periphery of the area frozen in about the same period of time as with tar alone. No warts appear to develop in the frozen area itself. The warts produced in mice treated with carbon dioxide snow and tar do not grow as rapidly, nor become malignant as soon, as those produced by tar alone.

AUTHOR'S SUMMARY.

SKIN REGENERATION AND CANCER. R. J. LUDFORD, Brit. J. Exper. Path. **10**: 193, 1929.

Repeated scarification of an area of the skin of the mouse does not result in an aberration of the process of repair nor induce cancer. An area of the skin that has been the site of repeated injury and repair is not more susceptible to the carcinogenetic action of tar than the normal skin.

AUTHOR'S SUMMARY.

STUDIES ON THE BEHAVIOR OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMPLANTED TUMORS. BRUNO BORGHI, Tumori **3**:289, 1929.

According to Borghi, a study of the reticulo-endothelial system by means of vital staining of animals inoculated with tumors demonstrates that the animals carrying recent tumors show a hypertrophy and hyperplasia of the reticulo-endothelial system. This is particularly noticeable when the tumors develop slowly. After full development of the tumors, the reticulo-endothelial system undergoes atrophy. The author concludes that besides possessing many other functions the reticulo-endothelial system participates in the defense against new growths.

W. OPHÜLS.

CONGENITAL ADENOMA OF LUNG AND HYDROPS UNIVERSALIS. P. ESCH, Arch. f. Gynäk. **133**:32, 1928.

A case of congenital adenoma of the lung in an infant with universal hydrops and hydamnion is reported. The tumor is considered as a hamartoma. Five reports of similar cases were found in the literature. A common cause for both conditions could not be established.

W. C. HUEPER.

THE VAGINAL PAPILLARY SARCOMA OF THE CHILD. K. ADLER, Arch. f. Gynäk. **133**:100, 1928.

A papillary fibro-epithelial tumor mixed with immature muscle cells and located in the vagina of a 2 year old girl is described. A review of sixty previous reports of cases and a discussion of the symptomatology and pathology of these tumors are given. They recur after removal, but form metastases only in the regional lymph nodes. The prognosis is extremely bad; only one case in which cure occurred is on record.

W. C. HUEPER.

THE HISTOLOGIC DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX. W. SCHILLER, Arch. f. Gynäk. **133**:211, 1928.

Among 135 cervices of uteri removed for reasons other than carcinoma, Schiller found 4, or 2.96 per cent, that showed beginning carcinoma. The uteri were from women in the climacteric or postclimacteric age. These cancers were not detected before operation, in spite of repeated previous clinical examinations. Periodical examination of women therefore does not represent a final solution of the problem of the early recognition of carcinoma of the uterine cervix. The early uterine carcinoma is histologically characterized by a sudden change of the normal stratified squamous epithelium into an atypical, polymorphous, anaplastic epithelium. It may possess plump, irregular papilli of varying size, which may perforate into glands. A thickening of the epithelium may be present, but it is never marked. The sharp line of demarcation between normal and pathologic epithelium is usually oblique, extending more into the basal layer than into the

superficial zone of the normal epithelium. This carcinomatous coat can be explained only as a transformation of normal epithelium of the basalis into malignant cells, as there is no evidence of any destructive growth of the malignant epithelium, such as the presence of detritus and leukocytes. Special pathologic metabolic products of the cancer cells spread by way of the intercellular bridges to the adjacent cells, effecting a malignant change of these cells. The predominance of this process in the cells of the basal layer is responsible for the oblique shape of the line of demarcation. Disposition toward tumor is only present in embryonic cells or cells with embryonic qualities (basal cells). Ulcers in the carcinomatous region are secondary changes and not the primary cause of the cancer. These cancers not only grow by transformation of normal cells of the basalis, but also by direct proliferation of the malignant cells. Early carcinomas do not show any infiltrative growth. The transformation of normal cells into malignant cells is a sudden and not a gradual process. Only lesions which invariably become malignant should be called precancerous. He includes in this group leukoplakia of the tongue and mouth, but states that in only from 60 to 75 per cent of the cases does it become malignant. He regards Bowen's dermatosis as definitely malignant. The histologic evidence of early malignancy consists in the following observations: The nuclei of the basal cells are smaller than normal, plump, oval or round and located at different levels in the cells. The cells do not form a regular, single layer, but are somewhat irregularly placed, some lower, some higher, producing the impression of stratification. The line of demarcation against the connective tissue is always sharp. The basement membrane is absent in the cancerous region and thickened in the parts of the normal epithelium adjacent to the malignant portions. The differentiation between basal cells and cells in the spinous cell layer is indistinct. There is not any or only an incomplete transitional cell layer. Cells in this layer resemble usually the atypical basal cells. They have a small amount of cytoplasm and are closely packed. The cell outlines are indistinct. The cells are irregularly arranged, and are irregular in size and shape and stainability of cytoplasm and nuclei. The number of nuclei is increased. Mitoses may be frequent and atypical. The superficial layers of the cancerous coat do not show the degenerative changes present in normal epithelium. In several cases, the coat consisted of polygonal, polymorphous, large, spinuous cells that stained deeper than the normal epithelium. They represent a more highly differentiated type of cancer cell.

W. C. HUEPER.

EXPLANTATIONS OF HUMAN TISSUES AND TUMORS. K. HEIM, Arch. f. Gynäk. **134**:250, 1928.

Explantations of fetal tissues (spleen, heart, brain, skin, ovary, endometrium) were successfully done. Amnion and chorionic villi could be constantly cultured. Chorionic villi did not grow after the fourth month of pregnancy. Growth of syncytial elements was never observed. Langhans' cells originate apparently from mesoblastic elements. They produced large masses of epithelioid cells in the cultures. Explantations of adult tissues were made from peritoneum and endometrium. Peritoneal elements could be successfully cultured only during an early part of pregnancy. Endometrium grew well, but only from the basal parts. The significance of this observation for the implantation theory of endometriosis is emphasized. Cultures of decidua were only successful up to the fourth month of pregnancy. Tissues of chocolate cysts, and carcinomas of corpus and cervix uteri and ovary were successfully explanted. The degree of differentiation obtained by the cells in the culture is evidently the result not only of a predetermined cellular quality but also of environmental conditions.

W. C. HUEPER.

PRODUCTION OF THE FLEXNER-JOBLING TUMOR BY FILTRATES. R. ERDMANN, Ztschr. f. Krebsforsch. **27**:69, 1928.

Using a stock of closely inbred rats of apparently high susceptibility to the Flexner-Jobling tumor, Erdmann produced similar tumors in twelve of thirty rats

inoculated, using for the inoculation cell-free filtrates of the tumor. Nine of these animals had been subjected to preliminary injections of India ink.

H. E. Eggers.

Immunization Processes in Malignant Tumors. C. Lewin, Ztschr. f. Krebsforsch. **27**:138, 1928.

Lewin regards such immunity as has been obtained against malignant tumors as due to the production of nonspecific antibodies formed during the metabolic stimulation that follows nonspecific protein therapy. This immunity is associated with a heightening of the leukocyte content of the blood.

H. E. Eggers.

Rous Sarcoma of Fowls. E. Fraenkel, Ztschr. f. Krebsforsch. **27**:150, 1928.

From his experiments, Fraenkel concludes that there can be no question that the Rous sarcoma may be produced by cell free material. He disagrees with Gye's conclusion that a second excitant is necessary, since the filtrable agent alone in sufficient quantity produces tumor. In all respects, this agent conducts itself as a ferment; it is associated with the euglobulin portion of the albuminous content of the filtrate. To meet all the requirements of the phenomena of the action of this agent, it would appear necessary to regard it as a transferable, reproducing ferment, similar to the bacteriophages.

H. E. Eggers.

Metastasis of Adenocarcinoma to the Choroid. A. Zamenhof and M. Plonskier, Ztschr. f. Krebsforsch. **27**:217, 1928.

The authors report a case of metastasis to the choroid of the eye of what clinically was almost certainly a primary carcinoma of the stomach. In addition, there were evident symptoms of cerebral metastasis.

H. E. Eggers.

Studies of Cancer-Producing Agents. C. C. Twort and H. R. Ing, Ztschr. f. Krebsforsch. **27**:308, 1928.

A study of the cancer-producing action of various oils showed that while sperm oil was apparently innocuous, the petroleum oils were dangerous to a certain degree, while shale oils compared well with coal tar. Of the petroleum oils, the high-boiling fractions showed the greatest toxicity, while the shale oils showed a wider range in this respect, the most active fraction being that of low boiling point. The exciting agent could be concentrated by means of methyl sulphite or ethyl alcohol, while diminution of the action, in part, could be accomplished by treatment with sulphuric acid or oxidizing or reducing agents. The most active substance studied by them was a synthetic tar prepared from pine. With this, most of the toxic material distilled over at from 200 to 300 F., with a pressure of 3 mm., and could be extracted with ethyl alcohol.

H. E. Eggers.

Etiology of Uterine Cancer. G. G. Ter-Gabrielian, Ztschr. f. Krebsforsch. **27**:362, 1928.

A study of the cases of uterine cancer appearing at the Butyrki-Ambulatorium at Moskow during the last five years (194 cases) led the writer to the following conclusions: The cases present no support for the infection or heredity theories of tumor inception. The most essential factor is chronic irritation, traumatic, chemical or thermal. In the female, the uterus is the most frequently attacked organ; frequent factors here are the complications of birth and induced and incomplete abortions; multiple normal deliveries cannot be regarded as a factor. Aside from irritant factors, an individual predisposition must be recognized.

H. E. Eggers.

EFFECT OF THE SPLEEN ON TUMOR GROWTH. B. E. BRUDA, Ztschr. f. Krebsforsch. **27**:380, 1928.

The writer found that when, in experiments in vitro, tumor tissue of mouse was cultivated in the plasma of splenectomized rats, there was an enhancement of growth. He concludes that in the normal animal protective substances against tumor growth may be of splenic origin.

H. E. EGGERS.

ORIGIN OF CARCINOMA OF THE LIVER AND PANCREAS IN ASSOCIATION WITH DISTOMATOSIS. M. G. RUDITZKY, Ztschr. f. Krebsforsch. **27**:402, 1928.

There is here reported a case of primary carcinoma of the liver or pancreas, in association with a severe infestation with *Opisthorchis felineus*. The writer regards the association as unquestionably one of effect and cause.

H. E. EGGERS.

CONTRIBUTION TO THE STATISTICS AND CLINICAL OBSERVATIONS OF PULMONARY TUMORS. E. SCHOENHERR, Ztschr. f. Krebsforsch. **27**:436, 1928.

In Chemnitz since the war there has been an undoubted increase of malignant tumors, especially of pulmonary cancer. The proportion of this to the total incidence of carcinomas is here the highest in Germany, a fact he ascribes to the great use of motorized vehicles, with resultant contamination of the air.

H. E. EGGERS.

METASTASIS OF A UTERINE CARCINOMA INTO A RENAL HYPERNEPHROMA. A. WALTER, Ztschr. f. Krebsforsch. **27**:451, 1928.

In a woman dying of uterine carcinoma with metastases to the liver, there was also a renal tumor that grossly and microscopically appeared to be an undoubted tumor of the Grawitz type. In this tumor were found islands of carcinomatous growth identical with the uterine metastases in the liver.

H. E. EGGERS.

THE AGENT OF THE ROUS SARCOMA. E. FRAENKEL, Ztschr. f. Krebsforsch. **27**: 467, 1928.

Attempts at the cultivation in vitro of the filtrable agent of the Rous sarcoma were unsuccessful, although the agent remained active after seven days' incubation at 37 C. in sterile bouillon. While reducing agents did not affect the activity of the filtrate, this was rapidly destroyed by the introduction of oxygen.

H. E. EGGERS.

FREQUENCY OF CARCINOMA IN EPILEPTIC PERSONS. VOLLAND, Ztschr. f. Krebsforsch. **28**:15, 1928.

In 575 deaths of epileptic patients who were more than 40 years of age, the writer found a cancer mortality rate of 3.1 per cent which is about one third of the usual incidence in persons of similar age. The lower rate in epileptic persons the writer ascribes to the altered humoral and metabolic variations in that disease exerting a restraining influence on the development of cancer.

H. E. EGGERS.

TUBERCULOUS INFECTION OF TESTICULAR CARCINOMA. F. KLINK, Ztschr. f. Krebsforsch. **28**:38, 1928.

The writer reports a case of associated tuberculosis and carcinoma of the testis, in which all evidence favors the view that the carcinoma became secondarily infected. This evidence is: the absence of epididymal tuberculosis; the absence of tuberculosis in the noncancerous portion of the testis; the almost complete absence of tuberculous necrosis, and the scarcity of bacilli as indicating recent infection. A similar case has been reported previously by Sakaguchi.

H. E. EGGERS.

A Method of Isolating Tumors within and without the Organism. A. A. Krontowski, Ztschr. f. Krebsforsch. **28**:60, 1928.

The writer describes a method of so isolating tumors within the host as to secure the tumor free from contact with adjoining surfaces. This he accomplishes by introducing the fragment for inoculation into a kidney or portion of a kidney, dissecting this free to its pedicle, and enclosing the whole in a sterile gutta percha sac through which the pedicle enters. In this way the tumor grows with a single vascular supply, facilitating the study especially of metabolic changes in such growths.

H. E. Eggers.

Prostatic Carcinomas—Their Frequency and Their Metastases. R. Pürckhauer, Ztschr. f. Krebsforsch. **28**:68, 1928.

Metastases to bone were found in 54.5 per cent of the fifty-five cases of prostatic carcinoma on which this report is based. In the thirty-nine cases in which the prostatic carcinoma was evidenced by marked changes in that organ itself, the percentage was considerably higher, 71.8. As regards location of the metastases to bone, the vertebrae showed the most frequent involvement; twenty-seven cases.

In the great majority of the cases, the bone involvement was of osteoplastic type. Next in frequency of involvement came the femur and the pelvic bones. In these cases there was metastasis to internal organs in only twelve cases, and in only one case was there metastasis to an organ without metastasis to bone. Attention is called to the frequency with which the cancerous alteration of the prostate is so minor as to be overlooked, except in microscopic examination.

H. E. Eggers.

Medicolegal Pathology

Acute Arsenic Poisoning. Theodore L. Althausen and Lewis Gunther, J. A. M. A. **92**:2002, 1929.

Hair is one of the main channels for the elimination of arsenic from the body. The delayed appearance of arsenic in the hair, its relatively high arsenic content and the length of time during which this poison can be detected there make hair one of the most valuable objects for analysis in cases of suspected arsenic poisoning. The administration of sodium thiosulphate in the case in which it was given was accompanied by an increase in the excretion of arsenic in the air, urine and feces and by marked clinical improvement.

Authors' Summary.

Fractured Clavicle, Thrombosis of the Right Subclavian Artery, Cerebral Embolism. A. G. Yates and D. Guest, Lancet **2**:225, 1928.

In an epileptic woman, aged 41, the right arm and hand for some months were painful and weak, and when first examined the hand was cold and bluish; there was no pulse in the arm or hand. As she was about to enter the hospital, cerebral embolism occurred, and at the postmortem examination a short clot was found in the right axillary artery and one 4 cm. long in the first and second parts of the subclavian, beginning 1 cm. distal to its bifurcation. The embolism was in the basilar artery and was explained by a part of the clot in the subclavian getting into the right vertebral artery. Near the thrombosed vessels in the neck, there was an old ununited fracture of the right clavicle.

E. R. LeCount.

Death at Birth from Hemorrhage into the Thyroid Gland. Mutel and Morin, Ann. de méd. lég. **8**:157, 1928.

A woman, aged 28, the mother of two children, with whose birth there was no difficulty, found her third child dead about twenty-four hours after birth. This child also was born in normal labor and apparently was well when born. Because

of anonymous accusations, a postmortem examination was made, and the only alteration found anywhere was a hemorrhage into the thyroid gland. The gland was twice the normal weight, the hemorrhage entirely within the capsule, and in the other structures of the neck there was no evidence of injury.

It is well known that spontaneous hemorrhages into the suprarenal glands may cause death in both infants and adults. About seven deaths from hemorrhage into the parathyroid glands in infants from 3 to 6 months old have been reported. Similar hemorrhages into the hypophysis with corresponding serious consequences apparently have not been observed. Goiterous swelling of the thyroid gland due to hyperemia caused by passage through the birth canal is well known, and usually yields quickly to hot packs and other local treatment. Hemorrhages such as this reported by Mutel and Morin causing death are extremely rare. It was difficult to find any thyroid tissue microscopically, because of its mechanical displacement and destruction by the apoplexy in the gland.

THROMBOPHLEBITIS OF THE UPPER EXTREMITY FROM STRAIN. L. LOUIS-CAEN, Ann. de méd. lég. **8**:188, 1929.

Reports have been made of about thirty cases of edema of the hand and arm caused by venous obstruction which, in its turn, has followed some unusual effort, such as violent abduction and rotation of the arm occurring in a fall, or repeated unusual but less violent strains. The relation of the edema, which does not always prevent working, to insurance and compensation is important.

A good résumé of the more recent literature is given with the report of a case in a carpenter whose obstructed circulation was not traceable to any unusual exertion. If one is to conclude that the venous obstruction is due to violence, the edema or other evidence of obstruction should be evident not later than a few days after the injury, and the presence or absence of disease causing or contributing to the thrombosis should be carefully determined.

E. R. LECOUNT.

TRAUMATIC ASCITES. WITAS and PARRES, Ann. de méd. lég. **8**:239, 1928.

Three days after being dragged by a runaway horse and receiving many blows on the abdomen and legs, a man noted that his legs were cyanotic and his abdomen swollen. A physician then found fluid in the abdomen and subcutaneous abdominal veins dilated to compensate for an obstructed portal circulation. Five tappings of the abdomen yielded 60 liters (60,000 cc.) of ascitic fluid; death occurred ninety-six days after the accident.

At the postmortem examination, no cause for the ascites was found, but in the account of this examination, it is not apparent that the inferior vena cava, hepatic blood vessels, liver or intrahepatic branches of the portal vein were thoroughly examined.

E. R. LECOUNT.

POSTPONED DEATH FROM TRAUMATIC HEMORRHAGE INTO THE FOURTH VENTRICLE. RENOUX, Ann. de méd. lég. **8**:255, 1928.

A young man was found dead in bed fourteen or fifteen hours after a football game, with the bed clothes stained from what must have been projectile vomiting. A watchman in the hotel heard only profound snoring. The only symptoms the young man complained of after the game were slight photophobia and dizziness when he stood erect after sitting. The fourth ventricle was found full of blood, which had extended from a hemorrhage in the occipital lobe near the right lateral ventricle. There was a scalp contusion, but no fracture; the only injury anywhere was that of the head.

E. R. LECOUNT.

INDUSTRIAL DISEASES FROM RADIOACTIVE SUBSTANCES. M. DE LAET, Ann. de méd. lég. **8**:443, 1928.

After the inclusion of many personal observations with a review of the literature, the following conclusions are stated: Contact with radioactive substances or

with their radiations causes, independently of external lesions, leukopenia and erythropenia, lowered blood pressure, sterility and sometimes leukemia; the disturbances of nutrition are not as well known; these effects occur early and when once established are tenacious. Although there are some individual variations in susceptibility, no one escapes altogether when exposure is at all prolonged or repeated. When the leukocytes are reduced to 2,500 or 3,000 and the red cells to not less than 2,500,000 or 3,000,000, the prognosis is not necessarily grave. These disorders from radioactive substances constitute an occupational disease; in determining compensation, the question of sexual potency or of sterility is important. Prevention and protective measures are discussed rather than the matter of liability; laborers exposed to these dangers should be examined frequently.

E. R. LeCount.

Occupational Diseases Caused by Hydrocarbons and Their Principal Derivatives. M. Duvoir, Ann. de méd. lég. **8**:453, 1928.

About forty pages are devoted to enumerating the many harmful substances in this chemical group, some of them natural products, most of them obtained by technical processes of isolation or synthesis. And with their description, the author cites the occupations in which their harmful action is likely to be encountered; he also gives brief accounts of the diseases they cause. Among the latter, poisoning from benzene is well presented.

E. R. LeCount.

Origin of Thrombosis in Veins. H. Wildegans, Arch. f. Klin. Chir. **148**:592, 1928.

More water, residual nitrogen and lactic acid were found in the blood of the saphenous veins, especially in association with varicosities, than in the cubital veins of eighteen patients, all but two of whom were 40 years old, or older. No significant differences were demonstrable in the amounts of calcium, fibrinogen or thrombin. It is suggested that instead of emphasis being put on disturbances of the circulation, infection or alterations of the walls of blood vessels to explain postoperative thrombosis and embolism, attention ought to be directed to the modifications in the physical and chemical constitution of the blood.

In discussing this work of Wildegans, Nieden called attention to the increase of postoperative thrombosis and embolism in the earlier decades of life, as well as their actual increase. Schönbauer mentioned the slowness of clotting of blood in the portal vein, which takes fourteen minutes, as compared with eight minutes for the clotting of blood from the lower extremities, and the need of fluids after operations. Von Seeman spoke of the excess of globulin and fibrinogen in the blood after operations, their origin from wound exudates and damaged tissues and the way these substances rob red blood corpuscles and platelets of their electric charge; thus promoting agglutination and sedimentation. He referred to the value of dextrose and Ringer's solution in correcting the instability of the plasma caused by increase in globulin and fibrinogen and to the relatively greater increase of these in the blood of patients with cancer.

E. R. LeCount.

Accident, Multiple Myelomas and Insurance. M. Laesecke, Arch. f. Klin. Chir. **149**:123, 1928.

Complete paralysis of both arms was present the day after a blow had been received on the back of the head and neck by one of several iron plates that a man aged 53 was carrying while at work. When he entered the hospital fourteen days later, only portions of the fourth cervical vertebra were found by roentgen examination. The trauma had aided destruction of a vertebra already diseased with one of many myelomas in the bones, either then present or developing subsequently. In the decision of the questions of compensation and insurance, it was decided that the accident had been a contributory cause.

E. R. LeCount.

INCREASE OF POSTOPERATIVE THROMBO-EMBOLISM AND ITS CAUSE. F. PROCHNOW, Arch. f. Klin. Chir. **151**:99, 1928.

With a brief summary of the other published statistics of the remarkable increase in deaths from pulmonary embolism after operations, Prochnow reports thirteen deaths that occurred in the surgical clinic of Bakay at Budapest, eleven of them during the last five of the years from 1915 to 1927, during which they all occurred. The operations numbered 18,517. He divides cases of pulmonary embolism as follows: those in which death was unexpected and without any preliminary symptoms; those in which chest pain, dyspnea, cough and bloody sputum were observed, with death occurring in a few minutes or a few hours, and those in which there were similar symptoms followed by recovery or death much later from abscesses of the lungs or pyemia. In other respects, this résumé is like many others resulting from the observation of the increasing frequency of these deaths.

E. R. LECOUNT.

LACERATIONS OF THE ABDOMINAL ORGANS BY BLUNT FORCE. B. NEUKIRCH, Arch. f. Klin. Chir. **153**:23, 1928.

The spleen alone was torn in two bodies; the left kidney and spleen, in one body; the liver, urinary bladder and one kidney, each in one body; the ascending colon dorsally where it lies against the back wall of the abdomen and is not covered by peritoneum, in one body; the descending colon in the pelvis at the junction with the rectum, in one body; the transverse horizontal part of the duodenum, in one body; the small bowel, in three bodies, location not stated, but in one of the three the tear was attributed to an open hernial pouch; and finally, tears of the mesentery, in two bodies.

The author emphasizes that the loops of small bowel are able to move away and escape damage from blunt force and are usually torn at places such as the duodenojejunal junction, where they are fixed to the wall of the abdomen. He admits that when distended, the bowel is sometimes torn on being crushed because the content is not readily compressed and is unable to move along, the adjacent parts of the channel being also filled. Only one of the fourteen persons was a woman; death occurred in eight of the cases.

E. R. LECOUNT.

FRACTURES OF THE EPIPHYSES OF THE DISKS OF THE BODIES OF VERTEBRAE. G. SCHMOR, Arch. f. Klin. Chir. **153**:35, 1928.

In addition to the three centers of ossification, one for the body and one for each lateral half, there are a number of secondary centers from which a vertebra develops. The latter appear much later than the first, and unlike epiphyses of long bones, they are without much influence on the normal growth of the remainder of the vertebra. In a former report (Ueber bisher nur wenig beachtete Eigentumlichkeiten ausgewachsener und kindlicher Wirbel, Arch. f. Klin. Chir. **150**:420, 1928), Schmorl stated that epiphyses for the upper and lower disks of the body which face the intervertebral cartilages appear at the thirteenth year. He now reports the appearance of some of them at the eighth year. He found them in the seventh cervical and first thoracic vertebrae in lower disks, in the second thoracic in the upper, in the third, fourth, sixth and seventh thoracic in both and in the tenth thoracic only in the lower. It will be seen from this that they do not all appear at the same time. These disks, which ultimately unite with the remainder of the body of the vertebra, develop from separate centers, two in front and two behind, and their appearance is also discontinuous. The various stages of their development is important in reckoning the age of a person, but also with reference to both disease and injury. Schmorl mentions having once met with tuberculosis in one of the disk epiphyses, and in this article he reports fractures of three particular epiphyses.

One was a fracture of the upper border of the body of the eleventh thoracic vertebra sustained in the World War when the man was 20 years old and found

thirteen years later after he had died from tuberculosis. Schmorl found it after the skeleton was macerated. The broken segment was ventral, included about one third of the entire rim, and was displaced so as to lie lower than the remainder of the rim. After fracturing, it had healed displaced. The man consequently had this part of the vertebra as an ununited epiphysis in his twentieth year. The second case concerned a woman who died at 22 and who four years previously was injured. The fractured epiphysis was in the third lumbar vertebra. It is difficult to find these separate centers of ossification for the disks by slicing the vertebra, but they are easily found by roentgen examination, which, although useful, is not so necessary in the demonstration of fractures in the prepared bones.

E. R. LeCount.

Delayed Death from Cyanide Poisoning. W. Ernst, Deutsche med. Wchnschr. **54**:1373, 1928.

There are a few reports of death five, six or even thirty-six hours after poisoning with cyanides, and by some the prognosis is regarded as favorable when death fails to take place within one or two hours. This report by Ernst deals with death twelve days after the onset of symptoms which, at the time, were regarded as from poisoning. After the death, a report from the medicolegal institute was returned that the poisoning was from potassium cyanide. The patient was severely afflicted with epilepsy and presumably poisoned himself, although the source of the poison was not learned.

E. R. LeCount.

Icterus from Lead. C. Lewin, Deutsche med. Wchnschr. **54**:1450, 1928.

Poisoning with lead, according to Lewin, may cause a pale skin with slight yellow discoloration of the sclera and bilirubin of the blood demonstrable only by the indirect reaction of van den Bergh. In this group, only urobilin or urobilinogen are in the urine, no bilirubin. With more pronounced icterus, both reactions for bilirubinemia are obtained, and the stools may be pale. Still more pronounced are the cases of acute yellow atrophy due to lead. Two of this last variety with cases of both other forms are reported.

E. R. LeCount.

Deaths from Therapeutic Punctures of the Thorax. T. Fahr, Deutsche med. Wchnschr. **54**:1550, 1928.

In attempts to tap the pericardial sac, three deaths occurred because the heart was pierced with the needle. In two of these cases, the heart was compressed by blood in the sac so that death occurred; in the third, the sac was so torn that the patient, a 6 year old girl, died from the bleeding into the left pleural cavity. In one of the first two, the blood stained fluid in the pericardial sac amounted to 1,000 cc., the bleeding from the wound made by the needle in the heart having been added to a huge transudate previously in the sac.

Three other deaths were accompanied by wounds of lung tissue. One was that of a woman who as a result of heart disease had hydrothorax. After death, 1.5 liters (1,500 cc.) of blood was found in the left pleural cavity from a wound of the lung made one-half hour before death, when one liter (1,000 cc.) of fluid was withdrawn. The other two deaths in association with wounded lungs are not explained as satisfactorily by Fahr, because there was neither hemothorax nor any huge hemorrhages into the lungs. The symptoms accompanying one death suggest embolism of air into the coronary arteries or into both sets of vessels (see Rukstinat, G. J., and LeCount, E. R.: Air in the Coronary Arteries, J. A. M. A. **91**:1776 [Dec. 8] 1928); the symptoms preceding the other are not related.

E. R. LeCount.

Sequences of Penetrating Bullet Wounds of the Thorax. M. Ernst, Deutsche Ztschr. f. Chir. **206**:294, 1927.

Many interesting observations are reported in an account mainly devoted to the amounts of pensions to be given different former soldiers in the World War. The

patients came to the surgical clinic of Sauerbruch from all over Germany, and there it was decided whether the missiles or fragments of projectiles should be removed. In the case of twenty-four who came it was regarded as unwise to attempt operation, and two of these subsequently died. Operation was not undertaken for these two because there was too much tuberculosis present in the lungs. Of the remaining twenty-two, many recovered so as to return to their occupations.

A few refused operation; one of these died soon after from hemorrhage; in another the foreign body pulsated with the pulmonary artery. Eighty were operated on, and the foreign bodies removed. From the release of intrathoracic pressure after artificial pressure, two died; a third died from pneumonia, and one more from sepsis. Of thirty-eight whose operation was thoracotomy, twenty-three returned to work; of five others there was no information and the rest were partly healed. Ten of the thoracotomies were done for hemoptysis; sixteen for abscess of the lung. In many of the patients, symptoms did not appear until many years after they had been wounded. The first symptom was frequently hemoptysis following some unusual exertion. Abscess or gangrene or hemoptysis was the main symptom, but in some of the soldiers, the first symptoms did not develop until ten years after they had been injured.

E. R. LeCount.

Relation of Infection to Postoperative Thrombosis and Embolism. W. Stöhr and F. Kazda, Deutsche Ztschr. f. Chir. **208**:105, 1928.

With postoperative thrombosis established, subsequent local or generalized infection leads more frequently to multiple infarcts from the thrombus than to progressive extension of the thrombosis. Only two of thirteen deaths (15.33 per cent) were from huge emboli when there was a generalized infection or local infection of the wound; the other eleven were deaths from pyemia with multiple metastatic abscesses and septic infarcts. On the other hand, with no infection demonstrable by routine methods in eight bodies, there were seven deaths (87.5 per cent) caused by large emboli obstructing the pulmonary artery. When infection develops subsequent to the formation of clots in veins at some distance away from the site of operation, infarcts from small emboli are rare, and death results in more than half of the patients thus affected from large emboli which block the main branch of the pulmonary artery or its chief divisions. With no infection and thrombosis developing after operations in veins at some distance, death from embolism is frequent. This sort of death from large dislodged clots producing pulmonary embolism is as frequent without as with infection after operations.

Postoperative infection plays little part in causing progressive thrombophlebitis and sudden death from pulmonary embolism, and apparently is unconcerned with the formation of clots in veins at a distance. This last form of thrombosis is probably related to the disturbances of the bowels, and stomach following infection of wounds; also to constitutional peculiarities and the severe changes in metabolism which result from major operations. These conclusions resulted from a study of the records of 24,032 postmortem examinations, 20,654 with 134 deaths from postoperative embolism and twenty-four cases of thrombosis distant from the wound and in none of these twenty-four was there embolism of any kind; in a second group of 714 postmortem examinations thirteen deaths from embolism and in examinations made at a third place, all in Vienna, thirteen deaths from postoperative embolism in 2,664 necropsies. Stöhr was unable to find confirmation in this study for the opinion Aschoff expressed at the meeting of the German Naturalists in 1911 in Karlsruhe that thrombosis in veins quite removed from the wound is especially frequent after operations when infection is present.

E. R. LeCount.

Arthritis from Foreign Bodies in the Joints. O. F. Ehrentheil, Deutsche Ztschr. f. Chir. **208**:409, 1928.

In reporting removal of a needle from a knee joint treated for some time as tuberculosis, emphasis is given to the two forms of arthritis from foreign bodies

when no infection occurs: intermittent hydrops with metallic objects or fragments, and a second form with wood (sharp splinters, thorns, etc.) with a marked resemblance to hyperplastic tuberculous synovitis.

E. R. LeCount.

Relation of Injury to a Secondary Thyroid Gland Carcinoma of the Right Femur. E. Brinkmann, Klin. Wchnschr. **6**:1903, 1927.

Although no primary tumor was demonstrated, it was decided that the injury of the right femur had brought about the location there of thyroid tissue which produced an adenocarcinoma found by roentgen examination ten weeks after the fall, and subsequently verified microscopically. A piece was cut out for microscopic examination a week after the growth was demonstrated roentgenoscopically, and the tissue was again examined after amputation eighty-six days after the injury. The patient was a woman 45 years old. The thyroid gland was not altered in any way clinically demonstrable, nor any evidence obtained of other metastatic growths. Shortly before amputation, the femur broke where the growth was located.

E. R. LeCount.

Occupational Actinomycosis. Reckzeh, Klin. Wchnschr. **7**:2299, 1928.

The possibility that actinomycosis can be incurred independently of the occupation, threshing of rye, resulted in the refusal of petitions of the widow for compensation. The actinomycosis was abdominal, and it was claimed that the fungus was swallowed with dust from the grain, which got on the food. On the other hand, it is of interest that the German regulations for compensation for accidents sustained in various occupations prescribe payment of claims for anklyostomiasis acquired by laborers employed in digging tunnels.

E. R. LeCount.

Epilepsy Following Benzine Poisoning. G. Stiefler, Wien. med. Wchnschr. **78**:938, 1928.

Rendered unconscious by benzine vapors as he was busy in a tank for benzine, 13 feet deep, which was being emptied, a man, aged 35, suffered for many hours with asphyxia and tonic muscle spasma. He left the hospital after ten days, and typical epileptic attacks began three months later. They recurred every four to five months. He was not neuropathic and no history of epilepsy previous to the poisoning was obtained. It was assumed that changes in the brain from benzine had some causal relation to the development of the attacks.

E. R. LeCount.

Bismuth Poisoning from Beck-Paste. P. Torrione, Schweiz. med. Wchnschr. **58**:895, 1928.

An empyemic fistula was packed with Beck paste repeatedly, so that altogether 1,500 Gm. was used. This contained 150 Gm. of bismuth. Healing took place in two months. One month later, when stomatitis with superficial ulcers appeared, the fistula was reopened and 60 Gm. of a dark fluid was removed. Torrione says that bismuth poisoning in this way is frequent, and that measures to prevent it are: injecting only a little at a time; not using it in cavities freshly curetted, and never allowing it to remain in the cavities for more than five days. Injection of the paste should always be done slowly.

E. R. Le Count.

Technical

Comments on the Impregnation of Neuroglia with Ammoniacal Silver Salts. Nathan Chandler Foot, Am. J. Path. **5**:223, 1929.

The technic recommended by Kubie and Davidson, of the Rockefeller Institute, for preparing solutions of ammoniacal silver salts for the impregnation of brain tissue has been found, on trial, to give results commensurate with its chemically

correct basis and far superior to those obtained by using the more roughly prepared solutions now in general vogue. It is found that silver diaminohydroxide gives excellent results in the impregnation of astrocytes, while silver diaminocarbonate concentrates chiefly on the oligodendroglia and microglia. If mixtures of both salts are used, as is the case with most of the inaccurate methods now employed, the impregnation is of a more general nature, but inferior in its specificity to that obtained through the use of pure salts. If the 1 per cent neutral formaldehyde in general use for developing sections impregnated with either of these double salts be buffered with a little sodium carbonate, a definite improvement in the development of the sections follows; the impregnation is more uniform, is freer from incrustations and precipitates and shows more precise definition of the neuroglia. No one method is recommended, the reader being left to draw his own conclusions and choose for himself that technic which will suit his particular needs; it is considered that the subject is fully enough set forth to afford him an opportunity for devising his own procedure. The excellence of silver diaminohydroxide should, however, be stressed.

AUTHOR'S SUMMARY.

ISOLATION AND CULTIVATION OF THE MENINGOCOCCUS. RUTH GOSLING, J. A. M. A. **93**:611, 1929.

Excellent results are reported by Gosling in the use of a dextrose semisolid medium for the cultivation of the meningococcus. The medium is prepared by adding 1 per cent of dextrose and 0.25 per cent of agar to nutrient veal infusion broth, adjusting the reaction to p_H of from 7.2 to 7.4, and sterilizing 10 cc. amounts in tubes in the Arnold sterilizer one hour on two successive days. A large loopful of sediment from spinal fluid that has been centrifugated at high speed from five to ten minutes is inoculated into the upper half inch of the medium and a deep stab made. Growth appears in from eighteen to ninety-six hours, and the meningococcus has remained alive as long as two and one-half months.

TITRIMETRIC MICRODETERMINATION OF PHOSPHORUS IN SERUM AND FLUIDS. K. SAMSON, Klin. Wchnschr. **8**:1029, 1929.

With from 1 to 2 cc. of serum or fluid, the estimations are made by precipitating the phosphorus in a protein-free filtrate (trichloracetic acid) as molybdate, dissolving the precipitate after washing it free of acid in N/40 NaOH, and removing the ammonia by the addition of formaldehyde. Retitration with N/40 HCl determines the amount of N/40 NaOH utilized. The volume (in cubic centimeters) of alkali utilized, multipled by 0.0277, equals the milligrams of phosphorus in the sample. The original article should be consulted for further details. Accuracy is claimed to within about 1 or 2 per cent.

EDWIN F. HIRSCH.

Society Transactions

THE PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 14, 1929

HAROLD J. AUSTIN, *President*

MELANOTIC TUMOR IN LOPHIUS PISCATORIUS (ABSTRACT). HELEN INGLEBY.

A melanotic tumor is described as having occurred under the epithelium of Lophius piscatorius. It was a black warty growth which projected above the level of the skin. It consisted of large branched cells loaded with masses of pigment, which in most cases completely obscured the nuclei. These chromatophores were of the same type as those under the normal epithelium, but more irregular. The main mass of the tumor lay above the level of the skin, was unencapsulated and was sharply demarcated from the subcutaneous tissue. The tumor showed a tendency to spread laterally rather than downward; the lateral offshoots were more loosely arranged and hence not so clearly demarcated from the surrounding tissues. Connective tissue septums seemed to divide the tumor into lobules. Groups of small, rounded, compact pigmented cells surrounded by connective tissue sheaths were seen, but not explained. Blood spaces were seen in the central part of the growth, together with numerous blood vessels. Groups of inflammatory cells were situated well below the tumor and separated from it by a broad layer of connective tissue. A large nerve trunk was present below the tumor, but the Bielchowsky method revealed no nerve fibrils in the tumor itself or entering the tumor from the connective tissue below. This may have been due to the condition of the material and to the masses of pigment cells obscuring the field.

This tumor is probably the homologue of the pigmented mole in man, as is suggested by its structure and its position beneath the epithelium. The theories of origin of pigmented nevi are given in substantiation of this relationship.

The epithelial origin was first supported by Unna, who traced a progressive transformation of prickle cells of the epithelium into nevus cells. This theory has been proved by Dawson.

The chromatophore theory and the mesoblastic theory originated with Ribbert, who derived pigmented moles from mesoblastic chromatophore cells. Action, a recent exponent of this view, maintained that in colored races the cells of the basal layer appear pigmented only because of delicate pigmented processes belonging to the melanoblasts, which arborize around the columnar cells and bodies of which lie in the dermis. This theory is not accepted by the majority of workers, who think the pigment granules lie in the protoplasm of the cells of the basal layer and sometimes in the adjoining layer, as well as in the cells of Langerhans. The epidermal Langerhans cells are true melanoblasts and pass pigment to the other cells. Recent work has shown that chromatophores do not originate in the epiblast.

The neural theory was first suggested by Soldan; he found myelinated nerve fibers at the base of the tumor and running into it. He thought nevi were a form of neurofibroma. Masson thought nevi were derived from cutaneous nerve elements. He said the deeper part of the tumor consisted of a plexus derived from nerve fibers which are surrounded by a syncytium with numerous nuclei derived from the cells of the sheath of Schwann or from the supporting cells of the Wagner-Meissner corpuscles. The superficial portion arises from the cells of Langerhans and their homologues, the tactile cells of Merkel-Ranvier. Masson thought that the branched Langerhans cells are connected with cutaneous nerve endings, and that in the deeper structures nerve elements analogous to the tactile

corpuscles of Meissner are found. He accounted for the growth of nevi on the hypothesis that, owing to some malformation, the cutaneous nerve fiber is unable to reach its destination and so forms a plexiform neuroma, while the peripheral elements form a glioma. He pictures the early stages of nevus formation in which the epithelioid nevus cells arise from the cells of Langerhans in the epidermis.

The melanotic tumor found in Lophius piscatorius is probably the homologue of the pigmented mole in man. The chromatophore cells of cold-blooded animals are probably homologues of the Langerhans cells, which are the pigment producers of human epithelium. Proof of this and further study of Langerhans cells and chromatophore cells are needed. In fish, a close connection obtains between the chromatophore cells and the nervous system. In *Amphibia,* no such connection has yet been discovered. Masson believed such a connection to exist in warts. The origin of nevi and chromatophore tumors, whether from epithelial or from neural tissue, is still undecided, but is probably the same for both.

CHRONIC LIGNEOUS THYROIDITIS (NONSPECIFIC GRANULOMA OF THE THYROID). L. A. MARKLEY.

Chronic ligneous thyroiditis was first described by Riedel in 1896. Since that time about forty-five cases have been reported in the literature.

The clinical features may be summarized as follows: The condition occurs chiefly in persons over 40 years of age. The symptoms are those of constriction and pressure on the esophagus, trachea and recurrent laryngeal nerves. Dyspnea is the most common late symptom. There are no toxic symptoms and no myxedema. The goiter may grow slowly or may increase suddenly. The signs are those of well marked goiter, symmetrical or unilateral. The regional lymph nodes are not enlarged; the overlying skin is not adherent. The most marked feature is the extreme hardness. The surface may be smooth or nodular. The basal metabolic rate is normal.

The present case is shown because of: (1) the difficulty in diagnosis; (2) the possibility of confusion with lymphoid tumor, carcinoma and Hodgkins' granuloma, and (3) the marked feature of atrophy of the glandular tissue of the thyroid.

Report of Case.—A white man, aged 65, complained of swelling in the thyroid region of the neck and dyspnea. He had hypertension, fibrillation and arteriosclerosis. The symptoms and signs were characteristic of the condition described. Total thyroidectomy was done. The Wassermann reaction was negative.

The weight of the thyroid gland was 350 Gm. The external surface was finely lobulated and yellowish white. The gland was uniformly hard. The cut surface showed distinct small lobulations; the trabeculae were not visibly emphasized; the color was yellowish white, with several small yellowish cystic areas.

The outstanding microscopic feature was the intense lymphoid infiltration, with follicle formation and germinal centers. There were small areas of eosinophilic infiltration. Among the lymphoid cells were small areas of intact acini, varying greatly in size. These were filled with colloid. The majority of the acini had lost the granular appearance; many under low power appeared like giant cells because of the desquamation and fusion of the acinar epithelium; others had the appearance of proliferating epithelial cells in roughly glandular structure. The lumina of some of the acini contained desquamated epithelial cells and lymphocytes. There were thick strands of fibrous tissue, from which extended finer strands, enclosing degenerating acini and lymphocytes.

In conclusion, the features characteristic of Riedel's struma were noted: (1) extreme lymphoid infiltration, with follicle formation; (2) glandular acini in all stages of degeneration, false giant cell formation, diminution in colloid content, cellular infiltration of the lumina of the acini; (3) increase in the amount of connective tissue, fibrosis and hyalinization; final stage of scar formation, with small foci of lymphocytes and an occasional acinus.

THYROID GLAND AND GROWTH. FREDERICK S. HAMMETT.

The growth reactions of the body and organs to thyroid deficiency were reviewed in the light of the factors contributive to alterations in the level of thyroid activity. The possible relation of these to long time, unidirectional shifts in environment from the evolutionary point of view was discussed. The paper as a whole was published in the *Quarterly Review of Biology* for September, 1929.

THE INFLUENCE OF SPLENECTOMY ON THE LEUKOPENIA INDUCED BY THE INJECTION OF CERTAIN FOREIGN SUBSTANCES. ISOLDE T. ZECKWER.

Doan, Zerfas, Warren, and Ames (*J. Exper. Med.* **47**:403, 1928) recently reported interesting experiments in which they found that sodium nucleinate injected intravenously into rabbits resulted in marked leukopenia in the peripheral blood, which lasted for a number of hours and which then was succeeded by leukocytosis. They believed that during the peripheral leukopenia, the leukocytes collected exclusively in the spleen, as indicated by leukocyte counts made on the blood from the viscera, and by their finding that after splenectomy, sodium nucleinate resulted in no period of leukopenia, and that leukocytosis then began within a period of time from one half to one sixth of that required in animals in which the spleen was intact.

It seemed of interest to determine whether these observations of the effect of splenectomy applied to the reaction to foreign substances in general or only to the reaction to the specific substance sodium nucleinate. If the spleen should have such a function as storing and then discharging leukocytes, it would be of as great significance as the mobilization of red cells by the spleen from its reservoir, in conditions of great need, as demonstrated by Barcroft.

To determine this point, *Bacillus coli* vaccine was injected intravenously into rabbits, and leukocyte counts were made on the ear blood at frequent intervals after injection. The leukocytes fell abruptly and remained at a low level for several hours. The curves thus obtained were compared with curves obtained after injection of vaccine into the same animals at different times after splenectomy. It was found that splenectomy had no effect on the degree of leukopenia, or on the time of the rise of leukocytes after the leukopenic period.

These results necessitated a reinvestigation of the effects of splenectomy on the leukocyte changes following the injection of sodium nucleinate. Doan and his associates used sodium nucleinate in doses of 1 Gm. per rabbit. When this dosage was used in the present experiments, the animals showed marked circulatory depression. It was found that a much smaller dose, 0.1 Gm. was just as effective in producing leukopenia, and resulted in no obvious vascular changes, so that the animals could be bled readily, and this dosage was well tolerated, so that injections could be repeated frequently for comparison. It was found that in every animal used, splenectomy did not prevent the occurrence of a leukopenia following injection of 0.1, 0.5 and 1 Gm. The time of the rise in leukocytes varied greatly on different occasions in the same animal before splenectomy, and there was no evidence that splenectomy resulted in a more rapid return rise of the leukocytes than the same animals had shown before splenectomy.

With a dose of 1 Gm., the blood pressure fell to a low level on injection of sodium nucleinate, and this low level was maintained for a long time. With a dose of 0.1 Gm., there was a transient fall in blood pressure, but a rapid return to normal, and the leukopenia was maintained, while the blood pressure remained at the normal level.

HISTOLOGIC GRADING OF TUMORS. STANLEY P. REIMANN.

If a surgeon completely removes a malignant tumor, it will not recur and hence there is no need of grading it. If, on the other hand, fragments are left behind, the chances are overwhelmingly in favor of a recurrence. Since the question in grading tumors seems to be "Will the tumor recur?" it is obvious that the

answer is to be found in the gross aspect and not in the histologic. The most one can possibly do histologically is to estimate the rate of growth of any possible fragments left behind. Since these are present in unknown sizes, numbers and environment, it is impossible in the individual case, to make an accurate prediction. One can only say such and such results were obtained in a large number of cases.

The study of tumor grading includes malignant tumors of the breast, uterus, skin and mucocutaneous junctions. Certain statistical results have been obtained, but they are without value in individual cases except to say that the chances are thus and so. Full details are in preparation.

Regular Meeting, May 9, 1929

HAROLD J. AUSTIN, *President*

CHRONIC LYMPHATIC LEUKEMIA IN A GREEN MONKEY. E. P. CORSON-WHITE.

A case of chronic lymphatic leukemia in a green monkey was presented. This case was discovered at necropsy, when the blood was not in a condition that permitted reliable observation; the diagnosis, therefore, was based on the infiltrative character of the lesions, the absence of distinct tumors and the numerous mononuclear cells in the blood as seen in the sections.

A point of much interest in this animal was the mononuclear exudate at every point of inflammation, notably in the lesions of the jaw, in the erosions of the stomach and in the lesions of the intestines. Similar ulcerations in cases in man, have been reported, especially in the tonsils and the pharyngeal lymphoid tissue and in ulcerated Peyer's patches; these have been described as mononuclear infiltrations at points of inflammation or as purulent destructions of diffuse leukemic infiltrates, but these differ from the observations in the case in question in that the infiltrations occurred where there was normally lymphatic tissue.

The monkey had a great overgrowth of lymphatic tissue, a blood picture characterized by a preponderance of small type, deeply staining basophilic lymphocytes which gave a negative response to the stains for oxydases. The lesions in the separate organs were infiltrative, and there was an absence of any definite tumor formation — a combination that justified a diagnosis of chronic lymphatic leukemia similar to that found in man.

MYCOSIS IN LOWER ANIMALS. FRED D. WEIDMAN.

Owing to the extensiveness of his material, the presenter omitted the section of the paper which dealt with the domestic animals. Mycoses are well known to occur in them, and the frequency of communication to man thoroughly authenticated and described in works on veterinary and human medicine. He confined himself largely to the mycoses that he had observed in the Philadelphia Zoological Gardens; but at the same time, the occurrence in such lowly forms as insects and oysters was included, because as yet they had not been brought together into any one place in medical records. Lesions and micro-organisms were illustrated by lantern slides.

In the Philadelphia Zoological Gardens several cases of ringworm, or dermatomycosis, were met with. In the cases in two young Barbary apes just arrived from the dealer, *Trichophyton gypseum* was established as the cause. Attempts to reproduce the disease in an old horse were unsuccessful; younger subjects were much more liable to this disease, as in man. Ringworm was also encountered in a young chimpanzee. *Trichophyton gypseum* is one of the organisms capable of producing ringworm in man, and there is the obvious possibility of transmission.

Exfoliative dermatitis in the Indian rhinoceros *(Rhinoceros unicornis)* was observed. A yeast species, *Pityrosporum pachydermatis,* was isolated. This organism was closely related to *Pityrosporum ovale,* which is commonly assigned as the cause of seborrhea capitis and other seborrheas of man. The presenter found the same organism in a similar dermatitis of a rhinoceros in the New York Zoological Gardens.

Superficial dermatophytosis in the axilla of a monkey was described. This resembled the seborrheic dermatitis of man, but while the organism was analogous to *Pityrosporum ovale,* there were differences adequate to separate them.

But one other instance of ringworm in wild animals appears to be on record, that of Pinoy, who described a case caused by *Epidermophyton simii.*

Thrush occurred in four Mississippi kites. The condition extended from pharynx to esophagus and stomach. *Oidium* was determined but not the species. Thrush was once encountered in the parrot.

Favus has not been met with in the zoological garden, but reports of its occurrence in wild rats and mice are rather widely scattered through dermatologic literature.

Actinomycosis has been met with in the Philadelphia garden in tapirs, a sable antelope and a cebus. The latter two recovered under potassium iodide therapy.

Kangaroo disease, preeminently of the jaws, and analogous to actinomycosis, was caused by *Nocardia macropodidarum.* It had a greater tendency to generalization than actinomycosis and is a serious problem in the zoological garden.

Nocardiosis was seen in a skunk. This disease is primary usually around the jaws, which frequently become injured during fighting. The infection tends to generalize, producing extensive necroses in the lungs and elsewhere.

Aspergillosis is the most frequently met form of mycosis in the Philadelphia gardens — as many as thirty-four birds dying in a single year. Pigeons, parrots, ducks, eagles and penguins are liable. Flamingoes were concerned in an English zoological garden. *Aspergillus fumigatus* and *Aspergillus glaucus* were the common offenders.

Deep hyphomycosis was observed in sea lions. The writer believed that the organism concerned in this was the largest that has even been described as a pathogen in animals; a single cell as large as 30 microns in diameter and 250 in length. The form, in general, was that of a branching fungus, but the method of reproduction was solely by transverse fission, and the writer felt that it might well be one of the *Algae.* The disease produced was a chronic granuloma with much necrosis and suppuration.

Spontaneous mycosis has been described as occurring in rabbits that were being employed for experiments. This was a report from the literature, and was only cited because it is of importance to laboratory workers.

Among the less spectacular mycoses, but having nevertheless some bearing on the interests of man might be mentioned those of bees due to aspergilli, which effected serious economic losses. Houseflies are liable to a disease produced by *Empusa muscae,* which kills these insects in the autumn. Infections fatal to mosquitoes were produced by *Coelomomyces stegomyiae* and *Zographia notonectae. Aspergillus glaucus* and *Aspergillus niger* may be fatal to the larvae of both *Culex* and *Anopheles.* The giant ants of Africa and elsewhere, which are a nuisance to man, were liable to an infection by *Cordyceps myrmecophila. Nocardia matrychoti* in oysters had occasioned serious economic losses in France.

SOME OBSERVATIONS ON THE COMPARATIVE ANATOMY OF THE BREAST. J. W. WAINWRIGHT.

A lantern demonstration was given, showing isolated points in connection with the mammary glands and nursing habits of animals and both savage and civilized women. Among the points illustrated were: the relation of the number of mammary glands and the number of young at birth; the positions of the glands in various animal species with explanations as to why, if only one pair of glands

remained, it should be either in the groin or in the pectoral region; the protected position of the nipples in certain animals, for example the whale and the seal; different racial habits of nursing and holding the baby and instances of women, mostly savage, nursing young animals such as pigs, puppies, etc., out of economic necessity.

SOME OBSERVATIONS ON THE DISTRIBUTION OF PARASITES IN MAMMALS WITH THE REPORT OF SOME NEW FORMS. W. P. CANAVAN.

Many well known round-worms having a worldwide distribution and many rare forms were reported. Several changes in systematic position of known forms and confirmation of others were made. Numerous new host-parasite relations and new localities were recorded. Significant cases of parasitism met with yearly were discussed, including the occurrence of superparasitism. No new groupings or combinations were proposed. Emended descriptions of *Trypanoxyuris trypanuris* Vevers (1923) and *Cyrnea colini* Cram (1927) were given. A new name is proposed for *Dirofilaria subcutanea* Linstow (1899), Boulenger (1920) designating it as *Dirofilaria hystrix* nom novum. *Eustrongylides* larvae Ciurea (1924) are included under a new species *Eustrongylides wenrichi*, preadult stages of which were found in a stream pike *(Esox americanus)*, nine-spined sunfish *(Enneacanthus gloriosus)*, calico bass *(Pomoxis sparoides)*, brook trout *(Salvelinus fontinalis)*, and a frog *(Rana catesbiana)*. New species described are *Acuaria (Dispharynx) resticula* from the groove-billed ani *(Crotophaga sulcirostris)*, *Ascaridia petrensa* from partridge *(Caccabis saxatilis chukar)*, *Dirofilaria spinosa* from porcupine *(Erethizon dorsatus)*, *Physaloptera multiuteri* from monkey *(Ateles ater)*, *Subulura pennula* from quail *(Callipepla squamata)*, *Spironoura procera* from terrapin *(Chrysemys rubiventris)* and the aforementioned *E. wenrichi*. The repository of types is the Zoological Laboratory, University of Pennsylvania. In all, there are 162 determinations in 38 genera and 56 species, including new ones, from 150 hosts involving 117 different host species.

Book Reviews

HUMAN HELMINTHOLOGY, A MANUAL FOR CLINICIANS, SANITARIANS AND MEDICAL ZOOLOGISTS. By ERNEST CARROLL FAUST, PH.D., Professor of Parasitology in the College of Medicine of Tulane University. Cloth. Price, $8. Pp. xxii and 616, with 297 illustrations. Philadelphia: Lea & Febiger, 1929.

The human body is subject to attack by a wide variety of parasitic organisms, including bacteria, protozoa, helminths and insects. The different degrees of attention which these groups of parasitic organisms have received from physicians is remarkable, as they have little relation to the importance of the several groups of parasites to the human race. Bacteria have long held the leading place, and are strikingly stressed in all medical schools; it would be difficult to count the number of excellent modern books on bacteriology. The animal parasites, on the other hand, have been more or less neglected, the protozoa somewhat less so than the worms. But among the protozoa are included the etiologic agents of such diseases as malaria, amebic dysentery, kala-azar and trypanosomiasis. The protozoa, however, have little cause for complaint if compared with the parasitic worms or helminths. In most medical schools a small fraction of one semester is devoted to a study of these organisms, and it is doubtful if the average medical man reads one article on helminthology to a hundred on bacteriology and protozoology.

It is natural, in view of the small amount of attention that is paid to the subject in medical schools and the paucity of articles on it in the most widely read journals, that medical men should greatly underestimate the importance of helminthology as a branch of human medicine. It is true that in many localities where modern sanitary conditions prevail helminthic infections have all but disappeared, but the diseases of people in foreign countries are no longer inconsequential to us. The human animal is today travelling farther, faster and oftener, by land, sea and air, than he has ever travelled before. Exotic infections will become established in new places, and imported sporadic infections of foreign origin will occur more and more frequently in places beyond their endemic limits.

It seems, therefore, reasonable to expect that physicians should know at least a little about diseases that affect millions of human beings, even if in a distant part of the world, and have available a source of information about them to which they can refer confidently when more detailed information is desired. In China, 100,000,000 people are yearly exposed to infection with the intestinal fluke, *Fasciolopis buski;* in Egypt, the vitality of the entire nation is sapped by schistosomes; in western Asia, one fourth of the population of innumerable villages is incapacitated for a month each year by guinea-worms; in every humid tropical and semitropical climate in the world, the vast majority of the inhabitants are infested with hookworms, including a high percentage of the school children in the southern states of the United States; even in parts of the United States there are localities where *Ascaris* and *Trichuris* affect more than half of the children and many of the adults; probably a minority of human beings, even in this country, get through life without affording food and shelter for pinworms (oxyurids). In addition to these there are to be considered the frequent occurrences of various tapeworm infections, trichiniasis, filariasis and a large list of minor infections from worms to which the human body is subject. In the seventeenth century 4 human worm parasites were known; in the early part of the nineteenth century there were 12; in Faust's book are listed 103, of which 30 are common human parasites.

Faust's work is strongly recommended as a reference book. Faust himself not only has taught helminthology to physicians and zoologists for nearly two

decades but has made highly important original contributions to knowledge in every important phase of the subject, and on all the important groups of parasites, and he is therefore qualified, as few others are, to write such a book as he has written. The information contained is thorough and up to date, and contains surprisingly few errors. It is not a mere sterile description of the worm parasites of man, which many books on parasites are; it contains accurate information on life histories, epidemiologic factors, pathology, diagnosis and methods of treatment and prevention. After some introductory chapters on general parasitologic subjects, such as interrelations of parasites and hosts, history, geographic distribution, the basis for scientific names and a discussion of literature, with a list of important books which deal with helminthology and of periodicals which frequently contain important papers on the subject, the author goes on to discuss the various groups of helminthic parasites — flukes, tapeworms and nematodes — first in general, and then in detail, giving the most essential facts of what is known concerning each species. The classification and systematic position of the parasites are carefully considered, but are largely segregated in separate sections, so that this phase of the subject, which is of more interest to zoologists than to physicians, does not encumber the text as much as it otherwise might. In the latter part of the book there are several chapters dealing with methods, which should prove useful. At the end of the several sections are given bibliographies of important papers dealing with the several parasites or groups of parasites, from which the reader can get a clue to the entire literature on the subject. In the matter of nomenclature, which has always caused much trouble in parasitology on account of its instability, Faust is, in the abstracter's opinion, a little ultramodern in a few instances, but there should be little difficulty in finding parasites under the names by which they are better known in medical literature, for synonyms are given and are included in the index.

The book is exceptionally well illustrated, a high percentage of the figures being original, which is unusual in a book of this sort. The arrangement and construction of the book are excellent and it is attractive in appearance. Both the author and the publisher are to be congratulated on a fine and valuable piece of work. It is a book which every physician would do well to include in his library, for, as intimated, it deals with a subject worth knowing something about, and there is no other book which can take its place as a comprehensive, authoritative, up to date treatment of human helminthology. The publication of the book is an occurrence of more than usual interest — it marks an important milepost in the progress of the subject with which it deals. Helminthology has advanced at astonishing speed in the last ten or fifteen years; it has, in fact, advanced faster in that period than any other field of medicine, so far as the reviewer is aware. Its progress since 1915 has been comparable with the years from 1880 to 1900 in bacteriology. It is, therefore, an ideal time for a book to appear which brings this scattered mass of information together, to make easier the paths of those who will in the future carry the subject further.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume 12. Pathology of the Acute Respiratory Diseases and of Gas Gangrene Following War Wounds. Prepared under the direction of Major General M. W. Ireland, Surgeon General. By Major George R. Callender, M.C., and Major James F. Coupal, M.C. Price, $3.60. Pp. 583. Washington, D. C.: United States Government Printing Office, 1929.

This is essentially an atlas. A little more than one half of the volume is filled with illustrations most of which occupy an entire page. These are supplemented by twenty-five colored full page plates. All the illustrations are from photographs, and in praising them only superlatives are appropriate. Together with some directions for staining microscopic preparations, the methods used in making the photographs are described in an appendix. The account of influenza and other respiratory diseases responsible for so many deaths among

American soldiers in cantonment hospitals here and in troops abroad is almost altogether an amalgamation of articles released during the war by the Surgeon General for publication in medical journals. In footnotes and in fine print, acknowledgment is made for the sources of this material. About thirty-six such articles are mentioned. Following this and scattered among the illustrations are about thirty pages by Major Callender in which the pathologic anatomy is discussed under the following headings: lobar pneumonia, interstitial pneumonia, peribronchial pneumonia, lesions associated with infection by *B. influenzae*, secondary bronchopneumonia, spreading bronchopneumonia (interstitial), acute bronchitis and pneumonitis without consolidation, secondary lobular pneumonia and interstitial lymphangitis with finally another subdivision on staphylococcal pneumonia from the report by Chickering and Park (*J. A. M. A.* **72**:617 [March 1] 1919).

This portion of the work is an elaborate legend for the illustrations. Many of the photographs, especially those of gross morbid anatomy, fairly glow with enlightenment. Great credit is due those who labored so faithfully during the war to prepare the museum material drawn on for these photographs. Involvement of the nasal cavity and its accessory sinuses is only casually mentioned. Such material probably was not secured in abundance.

The second section by Major Coupal on gas gangrene following war wounds conforms to reports of scientific studies as they appear in the best medical journals and monographs. There are numerous evidences of a thorough understanding of the subject by the author. For example, allusion is made in the bibliography to studies of gas gangrene and its bacteria carried out in foreign countries and other places outside governmental purview. The atlas feature also prevails in this section, since it has 10 of the colored plates and 144 other illustrations.

Publications from official bureaus and other branches of the government usually have peculiarities of make-up and material which put them in a different class from textbooks or journalistic literature. They are largely storehouses and often a prolonged search is necessary to find desired information. No such difficulty will confront those who consult this volume for visualizable conceptions of the diseases so elaborately portrayed.

THE ORIGIN OF MALIGNANT TUMORS. By THEODOR BOVERI, University of Würzburg. Translated from German by Marcella Boveri, with a foreword by Maynard M. Metcalf, Johns Hopkins University. Cloth. Price, $2.50. Pp. 128. Baltimore: Williams & Wilkins Company, 1929.

This is a translation by Boveri's wife, also a biologist, of the brochure "Zur Entstehung der malignen Tumoren" which was first published in 1914 by Gustav Fischer in Jena. When it appeared Boveri for a number of years had been recognized as one of the foremost authorities on the finer visible phenomena accompanying indirect cell division. By experiments with eggs of sea urchins he had succeeded in producing forms of pathologic karyokinesis corresponding to the multipolar and asymmetric division which occurs in many varieties of malignant tumors. He claimed that such abnormal methods of division of nuclei came about because wrong combinations of chromosomes formed the new nuclei. Application of the results of these studies of low forms of animal life to the genesis of tumors led to this work.

The trend of investigation of the origin of malignant tumors during the decade and a half since 1914 has been definitely away from problems of morphology toward others more closely related to the body as a whole. Modern conceptions of tumors are disposed to account for the anaplasia of von Hansemann and its corresponding deviations of nuclear division, studied so precisely by Boveri, as expressions of the characteristics possessed by tumor cells and not as causes of their rapid proliferation. The actual causes are being sought in disturbances of physicochemical balance and metabolism, in systemic disease and in familial

dyscrasias. At some future time tumor research perhaps may be directed again to peculiarities of tumor cells and to their unusual ways of multiplying. In any event there is no doubt that the relation these pathologic mitoses bear to those experimentally produced by Boveri will not escape recognition when the ultimate pattern of the etiology of tumor lies plainly before us.

Published as it was at the beginning of the war, but few copies of this work passed out of Germany. Its appearance in English is consequently bound to meet with general approval. Its discussion of chromosome irregularities is masterly and clear; the English rendition is carefully done with considerable evidence of an effort to simplify the somewhat involved and long German sentences. At present the chief value of the work is the charm of the critical thinking exhibited by the author in discussing evidence favoring, and that opposed to, his hypothesis. For younger men beginning a career of technical investigation in medicine, this presentation affords an unusual opportunity to become intimately acquainted with the care exercised by one trained in the ways of science.

A MANUAL OF EXTERNAL PARASITES. By HENRY ELLSWORTH EWING, United States Bureau of Entomology. Price, $4.50 (by mail, $4.66). 96 illustrations. Springfield, Ill.: Charles C. Thomas, 1929.

The main object of this book is to furnish brief sketches of the principal morphologic characters of the external parasites, their life histories and their natural relationships. The parasites in question are the mites, the ticks, the biting lice, the sucking lice and the fleas. This includes the rat flea concerned in the transmission of plague; the itch mite; the ticks of Rocky Mountain spotted fever, of Texas fever, and of spirochetosis of fowls; the sucking lice of relapsing fever, of trench fever and of typhus fever. In preparing the keys for identification, the large collection of parasites recently given to the National Museum by Dr. E. A. Chapin was found of great help. This collection is in the charge of the author. There is an abundance of good black and white illustrations, and the book contains a large amount of detailed and exact information clearly set forth, with valuable suggestions for control and protection.

Books Received

THE AUTONOMIC NERVOUS SYSTEM. By Albert Kuntz, Ph.D., M.D., Professor of Anatomy, St. Louis University School of Medicine. Cloth. Price, $7 net. Pp. 576, with 70 illustrations. Philadelphia: Lea & Febiger, 1929.

THE PATHOLOGY (PATHOLOGIC ANATOMY) OF THE EYE. By Jonas S. Friedenwald, A.M., M.D., F.A.C.S., Associate in Pathological Ophthalmology at the Johns Hopkins University; Pathologist of the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. Illustrated with 253 figures, mainly photomicrographs from the Pathological Collections of the Wilmer Ophthalmological Institute and the Army Medical Museum, by Helenor Campbell. Price, $4.50. Pp. 346. New York: The Macmillan Company, 1929.

DIAGNOSTIC VALUE OF THE "VACCINIA VARIOLA" FLOCCULATION TEST. By W. L. Burgess; James Craigie, and W. J. Tulloch. Medical Research Council, Special Report Series, 143. Pp. 43. Price, 1 shilling 3 pence, net. London: His Majesty's Stationery Office, 1929.

THE DEVELOPMENT AND GROWTH OF THE EXTERNAL DIMENSIONS OF THE HUMAN BODY IN THE FETAL PERIOD. By Richard E. Scammon, Professor of Anatomy, University of Minnesota, and Leroy A. Calkins, Professor of Obstetrics and Gynecology, University of Kansas. Price, $10. Pp. 365, with 73 illustrations. Minneapolis: The University of Minnesota Press, 1929.

MOLECULAR PHYSICS IN RELATION TO BIOLOGY. By M. Ascoli, Robert Chambers, A. de Coulon, F. G. Donnan, N. E. Dorsey, Leonor Michaelis, John H. Northrop, P. Lecomte du Noüy, W. J. V. Osterhout, William Seifriz and F. Vlès. Bulletin of the National Research Council, 69. Price, $3. Pp. 293. Washington, D. C.: National Research Council, 1929.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By Laurence H. Snyder, D.Sc., Associate Professor of Zoology, North Carolina State College, Raleigh; Committee on Blood Grouping, National Research Council. Price, $5. Pp. 153 with 28 illustrations and 5 plates. Baltimore: Williams & Wilkins Company, 1929.

HOOKWORM DISEASE: ITS DISTRIBUTION, BIOLOGY, EPIDEMIOLOGY, PATHOLOGY, DIAGNOSIS, TREATMENT AND CONTROL. By Asa C. Chandler, M.Sc., Ph.D., Professor of Biology, Rice Institute, Houston, Texas; recently Officer-in-Charge, Hookworm Research Laboratory, School of Tropical Medicine and Hygiene, Calcutta, India. Price, $5. Pp. 494, with 33 illustrations. New York: The Macmillan Company, 1929.

EDEMA AND ITS TREATMENT. By Herman Elwyn, M.D., Assistant Visiting Physician, Gouverneur Hospital, New York. Price, $2.50. Pp. 182. New York: The Macmillan Company, 1929.

INDEX TO VOLUME 8

The star (*) preceding the page number indicates an original article. No author entries are made except for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

INDEX TO VOLUME 8

INDEX TO VOLUME 8

THE ARCHIVES OF PATHOLOGY is published by the American Medical Association as a medium to advance the science of pathology in the United States and for the promotion of research and observation in this field.

Manuscripts for publication, books for review, and correspondence relating to contributions should be sent to Dr. Ludvig Hektoen, 637 South Wood Street, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF PATHOLOGY, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF PATHOLOGY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the publisher when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month — day of month if weekly — and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF PATHOLOGY is covered by copyright, but, as a rule, no objection will be made to its reproduction in reputable medical journals if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF PATHOLOGY, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF PATHOLOGY is published monthly. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

CONTENTS